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Datasheet for the decision of 24 February 2015

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Title of invention:
Complement pathway inhibitors binding to C5 and C5a without preventing the formation of C5b

Patent Proprietor:
Genentech, Inc.

Opponent:
AstraZeneca AB

Headword:
Antibody to C5 and C5a/GENENTECH

Relevant legal provisions:
EPC Art. 54, 56, 83

Keyword:
Novelty - (yes)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

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Catchword:

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Case Number: T 2332/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 February 2015

Appellant: (Opponent)	AstraZeneca AB 151 85 Södertälje (SE)
Representative:	Roques, Sarah Elizabeth J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Respondent: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 September 2010 concerning maintenance of the European Patent No. 1425042 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	K. Garnett

Summary of Facts and Submissions

I. The appeal was lodged by the opponent (hereinafter "appellant") against the decision of the opposition division to maintain European patent No. 1 425 042 in amended form. The patent has the title "*Complement pathway inhibitors binding to C5 and C5A without preventing the formation of C5B*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC), inventive step (Article 56 EPC), industrial application (Articles 52(1) and 57 EPC), patentability (Article 53(c) EPC) and under Articles 100(b) and (c) EPC.

III. In its decision the opposition division held that the subject-matter of the amended main request complied with the requirements of the EPC. Therefore, there was no need for the opposition division to decide on the pending auxiliary requests 1 to 6.

IV. With its statement of grounds of appeal the appellant submitted arguments why the subject-matter of the claims maintained by the opposition division lacked novelty, inventive step and was not sufficiently disclosed.

V. The patent proprietor (hereafter "respondent") filed with its response to the statement of grounds of appeal dated 24 June 2011, a main and auxiliary requests 1 to 6, which were all identical to the ones before the opposition division, and provided arguments why the subject-matter of the claims of the main request maintained by the opposition division fulfilled the requirements of the EPC.

Claim 1 of the main request reads as follows:

"1. An antibody or fragment thereof that binds to C5 and C5a, but does not prevent the activation of C5 and does not prevent formation of or inhibit the activity of C5b."

VI. Both parties requested oral proceedings. With its letter dated 19 December 2014, the appellant announced that it would not attend the oral proceedings and withdrew its request for oral proceedings.

VII. Oral proceedings before the board took place on 24 February 2015 in the presence of the respondent but in the absence of the appellant.

VIII. The following documents are cited in this decision:

D1: Klos, A. et al., (1988), J. Immunol. Methods, 111: pg. 241-252

D2: Amsterdam E. et al., (1995), Am. J. Physiol. (Heart Circ. Physiol. 37), 268: pg. H448-H457

D5: WO 01/15731

D6: Mulligan, M. et al, (1996), J. Clin. Invest., 98(2): pg. 503-512

D10: Makrides, S., (1998), Pharmocol. Rev., 50(1): pg. 59-87

D27: Declaration by Prof. A. Klos of 29 May 2009

D28: Experimental evidence relating to antibody "557" of DRG Diagostics

D33: Harlow & Lance, CHL Press , 1st edition, 1988, Chapter 5, pg. 72-77

D36: Exhibit C filed by respondent with its letter of 24 June 2011

D37: User's Manual for C5a ELISA manufactured by DRG Instruments GmbH from May 2004

D38: Declaration by W. Sänger of 12 January 2011

IX. The appellant's written arguments, as far as they are relevant for the present decision, may be summarised as follows:

Main Request

Claim 1

Claim interpretation

The feature "but does not prevent the activation of C5" of claim 1 would be interpreted by the skilled person to relate to an unaffected proteolytic cleavage of the complement 5 protein (C5) by the convertase either of the classical or of the alternative complement activation pathway but not by the convertases of both pathways. If the latter was meant then this would have been explicitly claimed.

The person skilled in the art would not interpret the feature "does not prevent formation of or inhibit the activity of C5b" of claim 1 in the sense that the C5b formation remained unaffected because the antibody claimed did not deplete C5 from serum upon binding.

Such a mechanism was neither suggested nor disclosed in the patent in suit. The only cause disclosed there for a reduced C5b formation was the impaired proteolytic cleavage of C5 into C5a and C5b by the convertases of the alternative and the classical complement pathways due to a sterical hindrance of a bound anti-C5/C5a antibody (see example 2 of the patent in suit).

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

If the subject-matter of claim 1 was interpreted to include antibodies that bound to C5 but lacked a C5 serum depleting activity, then the instructions in the patent were insufficient to obtain such antibodies. The patent disclosed neither that the claimed antibody had such a functional property nor assays allowing the skilled person to test and identify antibodies having this property.

Novelty (Article 54 EPC)

The subject-matter of claim 1 was not novel in view of the disclosure of several prior art documents.

Document D1 disclosed the two monoclonal human antibodies "561" and "557" which bound to C5 and C5a (see table 1, page 245). They had been commercially and thus publicly available since 2000 and thus before the priority date of the patent in suit (see declaration D27, point 3, paragraph (iii) in combination with document D37, page 4, point 2 and the declaration D38, point 1 with the attached invoice).

Although not disclosed, the antibody "557" had inherently the property of not interfering with C5 activation, i.e. the cleavage of C5 into C5a and C5b,

by the convertase of the classical pathway (see figure 2 of document D28). It was known that both the convertase of the classical and the alternative pathway cleaved C5 at the same site, which implied common structural characteristics. It was therefore reasonable to assume that the "557" antibody would also not interfere with the activation of C5 by the convertase of the alternative pathway.

Document D2 disclosed the monoclonal anti-porcine C5a "288-26F7" antibody that was obtained from the company Cetus, Emeryville, CA. The antibody was therefore publicly available before the priority date of the patent in suit (see page H449, column 1, fifth paragraph). The antibody also bound to C5 and did not inhibit the formation of the C5b-dependent membrane attack complex (MAC). This implied that it did also not prevent C5 activation, i.e. the cleavage of C5 into C5a and C5b (see page H454, column 1, first full paragraph).

Document D5 disclosed a C5a-derived nonamer peptide defined by SEQ ID NO: 16 for the preparation of anti-C5a antibodies by standard technologies and thus implicitly antibodies binding to this peptide (see table 1 on page 26, line 20 and claim 8). The peptide was three amino acids shorter than the 12mer peptide epitope recognized by the Mab137-26 antibody of the patent in suit, but otherwise identical. The conformation of the peptide of document D5 was linear while its corresponding conformation in the native C5a had a loop structure.

However, the antibodies prepared according to document D5 would also bind to their native epitope in C5a. Firstly, because the antibodies raised against the

linear peptides were screened by their binding to native C5a (see document D5, page 16). Secondly, the Mab137-26 antibody of the invention also recognised this epitope in both conformations (see patent in suit, figure 6) which implied a recognition that it is not conformationally restricted.

Inventive Step (Article 56 EPC)

The disclosure of the anti-C5/C5a antibody of document D2 that did not significantly prevent the formation of or inhibit the activity of C5b represented the closest prior art for the subject-matter of claim 1 (page H454, column 1, second paragraph; page H453, column 2, second paragraph).

The skilled person would have been motivated to provide further anti-C5/C5a antibodies to those disclosed in document D2 which selectively neutralised the activity of C5a without affecting the formation and activity of C5b, for example by the teaching of document D6 (see document D6, page 511, column 1, first and second paragraph). It was only a matter of routine to screen for and thus provide those antibodies.

Document D6 also disclosed that an anti-C5a antibody that cross-reacted with C5 reduced the serum levels of C5 and consequently its amount available for the generation of C5b, i.e. an antibody which affected the formation of C5b. However, in view of the general teaching in document D6, in particular on page 511, column 1, final paragraph, the skilled person would not be guided by this disclosure to prepare an antibody that bound to C5a, but not to C5. In fact, the skilled person would be well aware that the majority of antibodies that bound to C5a would also bind to C5 (see

document D4, passage bridging page 20 and 21). Hence, the subject-matter of claim 1 was obvious and lacked an inventive step.

X. The respondent's arguments, as far as they are relevant for the present decision, may be summarised as follows:

Main Request

Claim 1

Claim interpretation

The feature "but it does not prevent the activation of C5" of claim 1 would be interpreted by the skilled person such that the antibody did not interfere with any of the two known complement activation pathways involved in C5 activation, i.e. the classical and the alternative pathway.

The feature "does not prevent formation of or inhibit the activity of C5b" of claim 1 would be interpreted by the skilled person not only in the sense that the antibody did not impair the activation and thus cleavage of C5 by the convertase of both activation pathways to form C5b but also in the sense that the serum levels of C5 were not reduced by the antibody. The description disclosed the term "neutralize" exclusively in connection with the antibody binding to C5a but not with C5. The skilled person would have derived from this that C5 was not depleted by the antibody of the invention.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

The subject-matter of claim 1 did not refer to an antibody that bound to C5 but lacked a C5 serum depleting activity. Therefore the appellant's objection of an insufficient disclosure of the patent relating to a feature which was not present in claim 1 was irrelevant.

Novelty (Article 54 EPC)

The antibody of claim 1 was new over the disclosure in the prior art documents cited by the appellant.

The antibodies of documents D1 and D2 were not publicly available at the priority date of the patent and were therefore not prior art. These two documents in any event only disclosed that the antibodies did not interfere with the cleavage of C5 by the convertase of the classical complement activation pathway but were silent with respect to the convertase of the alternative pathway. It was also not to be expected that the antibodies did not impair the activity of the convertase of the alternative pathway in cleaving C5 because the convertases of both pathways were structurally different.

Document D5 neither actually disclosed antibodies raised against the peptide defined by SEQ ID NO: 16 nor assays that allowed the testing of these hypothetical antibodies for the functional properties of the antibody claimed. The peptide defined by SEQ ID NO: 16 and the epitope resulting thereof was moreover structurally and conformationally different from the epitope recognised by the antibody of the invention. An antibody raised against this peptide would therefore

not result in one which inevitably possessed all the functional properties of the antibody of claim 1.

Inventive Step (Article 56 EPC)

The anti-C5/C5a antibody of document D2 represented the closest prior art for the subject-matter of claim 1. The antibody of claim 1 in fact differed from that disclosed in document D2 in that it also did not interfere with the activity of the convertase of the alternative pathway in cleaving C5 while the antibody of document D2 disclosed this solely for the convertase of the classical pathway. This difference resulted in the provision of an anti-C5/C5a antibody that enabled the treatment of diseases caused by an excessive activation of the complement system through both the classical and the alternative pathways but without compromising the complement system's bactericidal activity.

The technical problem was thus the provision of an improved anti-C5/C5a antibody. The problem was solved by the antibody of claim 1.

The skilled person derived from the teaching of document D2 that the anti-C5/C5a antibody was cardioprotective by neutralising the activity of C5a alone, i.e. without concomitantly inhibiting the ability of C5b to form the MAC, which was, however known to be also responsible for myocardial damage. Starting from this document the skilled person would have therefore aimed at providing an antibody that at the same time neutralized both the activity of C5a and C5b, by binding to the cleavage site of the convertase on C5 and thus preventing the cleavage of C5 into its two active subunits.

Also the combined teaching of document D2 with that of document D6 did not render the subject-matter of claim 1 obvious. Document D6 reported an anti-C5a des-arg specific polyclonal antibody that also bound to C5, and thereby reduced the serum concentration of C5. A reduced C5 concentration affected automatically the formation of C5b because C5b is formed by the proteolytic cleavage of C5. The skilled person would have thus in the light of document D6 rather provided anti-C5a antibodies that did not bind to C5 to avoid its serum depletion.

The teaching of documents D2 and D6 would therefore rather lead the skilled person away from the solution provided by the subject-matter of claim 1, which was therefore inventive.

XI. The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained on the basis of one of the first to sixth auxiliary requests, all as filed with its letter of 24 June 2011.

Reasons for the Decision

Main Request

Claim 1

Claim interpretation

1. Claim 1 is directed to an antibody or fragment thereof that:

   (i) binds to C5, and

   (ii) binds to C5a, and

   (iii) does not prevent the activation of C5, and

   (iv) does not prevent formation of or inhibit the activity of C5b

2. The first issue between the parties is whether the feature "does not prevent the activation of C5" (i.e. feature iii, above) in claim 1 means that the antibody or a fragment thereof does not prevent, i.e. leaves unaffected, the activation of the complement 5 protein (C5) by both the classical **and** the alternative activation pathway of the complement system or whether it means that the antibody leaves unaffected the activation of C5 by only one of the two pathways.

2.1 It was common general knowledge at the priority date of the patent that the complement system had two independent pathways for its activation, the so called alternative pathway and the classical pathway. The first common compound in the activation process of the two pathways is the C5 protein. This protein becomes

activated by a proteolytic cleavage that enzymatically splits C5 into its two active fragments C5a and C5b. The cleavage of C5 is carried out by two different enzymes independently from each other, the so called convertase of the classical and the alternative complement activation pathway (see paragraph [0004] of the patent; document D10, figure 1).

2.2 The board considers that in view of this common general knowledge and in the absence of any indication in claim 1 to the contrary, the skilled person would understand that feature (iii) refers to the activation of C5 under normal circumstances, i.e. by both the classical **and** the alternative pathway. The board therefore concludes that in the context of claim 1 feature (iii) means that the proteolytic cleavage of C5 into C5a and C5b by the convertase of both complement activation pathways takes place in an unrestricted manner in the presence of an antibody bound to C5 and C5a.

3. A second issue is how the skilled person would understand the feature "does not prevent formation of or inhibit the activity of C5b" (i.e. feature (iv), above) in claim 1. In the respondent's view the formation of C5b depends on the cleavage of C5 into C5a and C5b by the action of a convertase (i.e. feature iii, see point 2 above) and the amount of cleavable C5 in the serum, which can be reduced by the action of a C5-depleting antibody. The respondent argued that the feature (iv) of claim 1 thus encompassed two meanings, namely (1) that the activation of C5 by the convertase of both complement activation pathways takes place in an unrestricted manner in the presence an antibody bound to C5 and C5a and (2) that the antibody bound to

C5 did not not reduce the amount of this protein in the serum.

4. The board notes that the only mechanism disclosed in the patent resulting in the "formation of C5b" is the one depending on the activation of C5, i.e. the enzymatic cleavage of C5 into C5a and C5b (see paragraphs [0004], [0023], [0027], [0028], example 2). The patent, however, neither discloses nor suggests that the C5 serum concentration *per se* or the absence of a C5 depleting activity by the anti-C5/C5a antibody of the invention has an effect on the C5b formation.

In the board's view, the skilled person would therefore only derive from the patent that the antibody of the invention does not prevent the formation of C5b because it does not interfere with the activity of the convertase of both activation pathways in cleaving C5 to form C5b.

5. The respondent also argued that the patent discloses a neutralizing antibody only with regard to C5a but not for C5 and that the skilled person would derive from this that the antibody of the invention binds to C5 without depleting it from the serum.

The board notes that C5 *per se* is an inactive protein which forms two active fragments only after cleavage, namely C5a and C5b. The former acts as a pro-inflammatory mediator (see e.g. paragraphs [0006], [0008] and [0011] of the patent) while the latter induces the formation of the lytic bactericidal membrane attack complex (MAC) (see document D10, figure 1, page 63, column 2, second paragraph). Accordingly, in the board's view, it makes sense that a neutralising activity of the antibody of the invention is only

disclosed for C5a but not for C5. Moreover, the board does not consider that the terms "neutralizing" and "depleting" have an identical meaning, because the former refers to an activity while the latter implies a physical removal of something from the system. Although the removal of a protein automatically results in the neutralisation of its activity, results the neutralisation of the activity of a protein not automatically in its removal from the system. The board therefore cannot agree with the argumentation of the respondent.

6. In view of the above considerations (see points 4 and 5), the board concludes that the skilled person would understand only that the feature "does not prevent formation of C5b" of claim 1 means that the activation of C5 by the convertase of both complement activation pathways takes place in an unrestricted manner in the presence of an antibody bound to C5 and C5a. Hence, an anti-C5/C5a-antibody either with or without a C5 depleting activity is not an embodiment of claim 1.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

7. Given the conclusion that the skilled person would understand the subject-matter of claim 1 in the sense that an antibody with a C5 depleting activity is not an embodiment of the claim (see point 6 above), the objection of insufficient disclosure raised by the appellant is considered irrelevant. No other objections of insufficient disclosure in relation to claim 1 of the patent as granted were raised by the appellant. The subject-matter of claim 1 of the main request therefore meets the requirements of Article 83 EPC.

Novelty (Article 54 EPC)

8. According to established case law the subject-matter of a claim lacks novelty only if it is directly and unambiguously derivable from the disclosure of the prior art (see Case Law of the Boards of Appeal, 7th edition, I.C.3.1, page 105, second paragraph).

9. Document D1 discloses the monoclonal human antibodies "561" and "557", both of which bind to C5 and C5a (see table 1, page 245). The experimental data of document D28 only disclose that the "557" antibody has the inherent property of not interfering with the cleavage of C5 into C5a and C5b by the "classical" convertase (see document D28, figure 2).

10. Document D2 discloses the monoclonal porcine "288-26F7" antibody which binds C5 and C5a and which does not inhibit the formation of the C5b-dependent membrane attack complex (MAC) (see abstract, page H449, column 1, last paragraph; page H453, column 2, third paragraph). The hemolytic complement assay used for analysing the formation of the MAC detects C5 cleavage by the classical complement activation pathway (see page H451, column 2, second paragraph; page H454, column 1, second paragraph; figure 5).

11. At the priority date of the patent it was known that the convertases of the classical and the alternative complement activation pathways are multi-subunit protein complexes with different structures. The "classical" convertase consists of the so-called C4b, C2a and C3b protein subunits while the "alternative" convertase consists of the so-called $(C3b)_2$, Bb and P

subunits (see paragraph [0008] of the patent; document D10,figure 1).

Although the two convertases are structurally different, both cleave C5 at amino acid position 74-75 to release the two active fragments C5a and C5b (see paragraph [0008] of the patent).

Before the convertases can actually cleave C5, they need to physically interact with C5, i.e. the enzymes must attach themselves to the surface of the C5 protein in the vicinity of the cleavage site. In view of their significant structural differences it cannot be ruled out that their respective interaction sites differ. It can be deduced from this that the binding site of an antibody on C5 that does not inhibit the activity of both convertases is not identical to the cleavage site of the convertases at position 74-75 but is somewhere in the proximity. From this and in view of the potentially differing interaction sites of the two convertases on C5 it can be inferred that antibodies may exist that interfere with the interaction of one convertase with C5 but not with the other.

Thus, the disclosure of an antibody that does not interfere with the activity of one convertase of one of the two pathways is not an unambiguous disclosure that the same antibody will not interfere with the convertase of the second pathway.

12. In view of the observations of point 11 above, the board concludes that the antibodies of documents D1 and D2 are different from the antibody of claim 1 because the documents do not unambiguously disclose that the binding of the antibodies to C5/C5a does not interfere with the C5 activation via the alternative complement

pathway. These antibodies therefore do not anticipate the subject-matter of claim 1 (see point 2.2, above).

13. In view of the board's conclusion in point 12 above, the issue of whether the antibodies of documents D1 or D2 were publicly available at the priority date of the patent has no relevance for the assessment of novelty of the antibody of claim 1. It is therefore not necessary for the board to reach any decision on it.

14. Document D5 discloses a C5a derived nonameric peptide defined by SEQ ID NO: 16 for the preparation of anti-C5a antibodies which are screened by their binding to C5a peptides (see page 16, lines 25 to 28; table 1 on page 26, line 20 and claim 8). The peptide defined by SEQ ID NO: 16 is three amino acids shorter than the 12mer peptide epitope recognized by Mab137-26 of the patent in suit (see figure 6) and has a linear conformation, whereas its corresponding conformation in the native C5a protein has a loop structure stabilised by a disulfide bridge (see figure of document D36, indicated by the arrow).

14.1 Document D5 neither discloses the actual preparation of an anti-C5a antibody directed against the peptide defined by SEQ ID NO: 16 nor a screening assay to assess whether such an antibody interferes with the C5 activation by any of the two convertases.

In particular, the ability to bind native C5a by an antibody raised against the peptide defined by SEQ ID NO: 16 is questionable in view of the common general knowledge that many antibodies raised against a linear peptide are unable to bind to their corresponding sequence in the native protein, if the native sequence

- as in the present case - has a different conformation (see document D33, page 74, first paragraph).

14.2 Hence, the disclosure of a peptide in document D5 to generate an anti-C5a antibody cannot be considered as an unambiguous disclosure of the antibody of claim 1.

15. The appellant argued that the antibody of document D5 has the functional properties of the claimed antibody since there is experimental evidence in the patent that the antibody of the invention recognises its epitope in different conformational states. Also, the anti-C5a antibodies of document D5, although raised against linear epitopes, are screened by their binding to native C5a and therefore necessarily bind epitopes in different conformations (see point 3.4.1 of the statement of grounds of appeal).

15.1 The board notes that the Mab137-26 antibody of the invention was raised against the native C5a protein while the hypothetical anti-C5a antibody of document D5 would be raised against a linear peptide. It is known that both antigens have a different conformation and a different structure (see point 14, above) and that the binding property of an antibody is determined by the antigen against which it is raised.

Consequently, in the board' view under the present circumstance no inference can be made from the binding properties of the Mab137-26 antibody of the patent on the binding properties of the hypothetical antibodies of document D5.

15.2 The board further notes that an antibody screening procedure using a particular antigen does not actively change or influence the binding properties of

antibodies in a sample raised against the same antigen. These are determined by the antigen against which the antibodies are raised (see point 15.1, above). The procedure rather selects those antibodies binding to the antigen used for screening thereby eliminating those that do not bind.

It is also highly questionable whether the antibodies raised against the linear peptide defined by SEQ ID NO: 16 of document D5 would be able to bind native C5a at all (see point 14.1, above). A screening procedure based on native C5a will under these circumstances therefore not necessarily isolate any anti-C5a antibodies.

15.3 Therefore the appellant's arguments are in view of the board's considerations in points 15.1 and 15.2 above, not persuasive.

16. In summary, the board concludes that the antibodies of documents D1, D2 or D5 do not anticipate the subject-matter of claim 1, which is therefore novel and complies with the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

Closest prior art

17. In 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.

18. The parties agree that the disclosure of document D2 represents the closest prior art and the board sees no reason to differ.

19. Document D2 reports on a study assessing the direct and indirect myocardial damage of the complement system during a heart attack in pigs. It discloses a porcine anti-C5/C5a monoclonal antibody with cardioprotective properties that neutralises the C5a-dependent cytotoxic activation of neutrophils and does not impair the cleavage of C5 into C5a and C5b by the convertase of the classical complement activation pathway (see abstract; page H448, column 1, last paragraph to column 2, first paragraph; page H451, column 2, second paragraph; page H453, column 2, second paragraph to page H454, column 2, line 2 and figure 5;). This anti-C5/C5a antibody thus represents the closest prior art.

Technical problem and solution

20. The antibody of claim 1 differs from the closest prior art antibody in that it also does not interfere with the C5 cleavage of the convertase of the alternative pathway (see point 2.2, above), thus allowing the treatment of a wider range of diseases. In view of the closest prior art and in view of the effects achieved by the anti-C5/C5a antibody of the present invention, the technical problem to be solved is formulated as the provision of an improved anti-C5/C5a antibody having a broader clinical applicability for the treatment of diseases caused by an excessive complement activation but without compromising the bactericidal activity of the complement system.

21. The board is satisfied that this problem is solved by the antibody of claim 1 in view of the experimental

data of the patent that disclose that the antibody allows C5 cleavage into C5a and C5b by the convertase of both the classical and the alternative complement activation pathways (see example 2 and figures 3 and 4).

Obviousness

22. The question to be answered is then whether the skilled person, starting from the anti-C5/C5a antibody disclosed in document D2 and faced with the technical problem defined above, would be motivated to provide the claimed anti-C5/C5a antibody in the light of the teaching of document D2 alone or in combination with the teaching of other documents, in particular document D6.

23. Document D2 discloses a monoclonal anti-C5/C5a antibody with a cardioprotective activity. The antibody achieves this effect by selectively neutralizing the activity of C5a. It does not however interfere with the enzymatic cleavage of C5 into C5a and C5b by the "classical" convertase (see page H454, column 1, second paragraph to column 2, line 2). It belongs to the common general knowledge of the skilled person that free C5b sequentially binds to the complement proteins C6, C7 and C8 to form the C5b-8 that catalyzes the polymerisation of C9 to form the MAC, i.e. C5b-9. The MAC has a pore-like protein structure that inserts itself into target cell membranes and causes cell lysis (see document D10, figure 1, page 63, column 2, second paragraph).

Document D2 reports in this respect that "*Complement-induced reperfusion injury associated with myocardial infarction has been attributed to the direct effects of*

the C5b-9 membrane attack complex and indirect actions mediated by the leukotactic properties of C5a" (see page H453, column 2, fourth paragraph) and thus that the myocardial damage caused by the complement system during an infarct situation in fact depends on two factors, namely (i) the formation of the MAC and (ii) an active C5a.

24. In the board's view, the skilled person would therefore derive from the teaching of document D2 that an improvement of the cardioprotective activity of the anti-C5/C5a antibody disclosed could be achieved if, besides the neutralisation of C5a, the content of C5b (which is essential for the formation of the MAC) could also be reduced or prevented. For the achievement of this goal, the skilled person would therefore prepare an antibody that blocks the cleavage site of the convertase on C5 to prevent the formation of both C5a and C5b. The skilled person would thereby generate an antibody that is different from the antibody of claim 1. Consequently, the antibody of claim 1 cannot be considered as obvious in the light of the teaching of document D2 alone.

25. There are, however, diseases caused by an excessive complement activation known in the prior art, wherein the presence of a functional MAC is nevertheless desirable, in particular if such diseases are accompanied by a gram-negative bacterial infection. Document D6 reports in this context about one study carried out in primates wherein a "*polyclonal antibody to human C5a des arg was protective in a model of sepsis (Escherichia coli) in nonhuman primates (44). However, the fact that animals infused with this antibody showed substantial reductions in blood levels of C5, as determined by immunoassay techniques (45),*

suggests that this antibody was reactive with intact C5, causing loss of serum CH50." (see page 511, column 1, lines 29 to 35).

25.1 The skilled person would infer from this passage of document D6 firstly that the polyclonal anti-C5a des-arg antibody was suitable for treatment of a bacterial sepsis because its binding did not impair the cleavage of C5 into C5a and C5b by a convertase, and thus allowed the formation of the MAC, which depends on the availability of C5b (see point 23, above). The skilled person would secondly infer from this passage that the formation of the MAC also depends on the amount of C5 available in the serum, which can be significantly reduced upon the binding of the antibody to C5, since less C5 will mean less available C5b after the cleavage of C5 and thus eventually less MAC. The document thus suggests the use of a "***selective*** *blockade of C5a* [by an antibody] *in the absence of interference with the production of the C5b-9*" (i.e. the MAC complex) (see page 511, column 1, lines 39 to 43). (Emphasis added by the board)

25.2 In the board's view, the skilled person would derive from the teaching of document D6 in the passages cited in the previous two paragraphs that (a) an anti-C5a antibody which does not interfere with MAC formation is attractive for the treatment of diseases induced by an excessive activation of the complement system and which are accompanied by a gram-negative bacterial infection but (b) but that it should be avoided that such an antibody binds to C5 as a whole.

26. The appellant argued that the provision of an anti-C5a antibody that does not bind to C5 was in contradiction to the general teaching of document D6 which suggested

that the antibodies should not impair the MAC formation. It was also contrary to the common general knowledge of the skilled person which taught that the majority of available prior art anti-C5a antibodies bound to C5.

27. The board notes that any reduction of the C5 serum concentration by the binding of an anti-C5a/C5 antibody as disclosed in document D6 will result in a reduced amount of available MAC required for the treatment of a bacterial infection (see point 24, above). The skilled person would have therefore not ignored the teaching of document D6 and would have provided an anti-C5a antibody that did not bind to C5. The board is also unable to agree with the argument of the appellant that the skilled person would have provided antibodies that bound to both C5 and C5a because the majority of the available anti-C5a antibodies had this property. The assessment of inventive step is purpose driven, requiring therefore a reason why the skilled person would ignore the teaching of document D6 that explicitly discourages the use of anti-C5a antibodies but that also recognises C5 for the reasons outlined above.

28. In the light of the disclosure in document D6, the skilled person would therefore be motivated to provide an antibody which exclusively binds to C5a. The antibody of claim 1 cannot therefore be considered as obvious in the light of the combined teaching of documents D2 and D6 either.

29. In summary, the skilled person, in view of the board's observations in points 23 to 28 above, would not be motivated to provide the antibody of claim 1. Hence, the board acknowledges the presence of an inventive

step and the subject-matter of claim 1 therefore complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated