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**Datasheet for the decision
of 27 October 2015**

Case Number: T 0907/10 - 3.3.04

Application Number: 02765050.6

Publication Number: 1432445

IPC: A61K39/395, A61P37/06,
A61P29/00, C07K16/28

Language of the proceedings: EN

Title of invention:

Treatment of chronic joint inflammation using an antibody
against the CD3 antigen complex

Patent Proprietor:

Isis Innovation Limited

Opponent:

MacroGenics, Inc.

Headword:

Anti-CD3 antibody Fab fragments for the treatment of
rheumatoid arthritis/ISIS

Relevant legal provisions:

EPC Art. 54

EPC R. 115

RPBA Art. 15(3)

Keyword:

Novelty of all requests - (no)

Decisions cited:

T 0609/02

Catchword:



Beschwerdekammern
Boards of Appeal
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Case Number: T 0907/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 27 October 2015

Appellant I:
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Decision under appeal:

**Interlocutory decision of the Opposition
Division of the European Patent Office posted on
2 February 2010 concerning maintenance of the
European Patent No. 1432445 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
 M.-B. Tardo-Dino

Summary of Facts and Submissions

- I. The appeal was lodged by the patent proprietor (hereinafter "appellant I") and the opponent (hereinafter "appellant II") against the decision of the opposition division to maintain European patent No. 1 432 445 in amended form. The patent has the title "*Treatment of chronic joint inflammation using an antibody against the CD3 antigen complex*".
- II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC) and under Article 100(b) EPC. The objection of lack of novelty was based *inter alia* on documents D4 and D7 (the respective documents are identified in section IX below).
- III. In its decision, the opposition division dealt with a main request, which consisted of the claims as granted, and an auxiliary request. It held that the subject-matter of claim 1 of the main request lacked novelty over the disclosure of document D7 and that the subject-matter of the claims of the auxiliary request complied with the requirements of the EPC (the respective document is identified in section IX below).
- IV. With its statement of grounds of appeal, appellant I re-submitted the requests dealt with in the decision under appeal.

Claim 1 of the main request reads as follows:

"1. Use of an anti-CD3 antibody for the manufacture of a medicament for the treatment of chronic joint inflammation, wherein the antibody consists of Fab or

F(ab')₂ fragments or is an antibody mutated in the Fc region to prevent binding to Fc receptors."

Claim 1 of the auxiliary request reads as follows:

"1. Use of an anti-CD3 antibody for the manufacture of a medicament for the treatment of chronic joint inflammation in rheumatoid arthritis, wherein the antibody consists of Fab or F(ab')₂ fragments or is an antibody mutated in the Fc region to prevent binding to Fc receptors."

- V. With its statement of grounds of appeal, appellant II submitted arguments why the subject-matter of claim 1 of the auxiliary request maintained by the opposition division lacked novelty, *inter alia* in view of the disclosure of document D4 (the respective document is identified in section IX below).
- VI. Appellant I and appellant II each replied to the other party's statement of grounds of appeal.
- VII. The parties were summoned to oral proceedings, but informed the board in writing that they would not attend.
- VIII. Oral proceedings before the board took place on 27 October 2015 in the absence of both parties as announced.
- IX. The following documents are cited in this decision:
- D4: CA 2224256
- D7: Utset et al., *Arthritis & Rheumatism*, 44 (9) Supplement: Abstract No. 237 (September 2001)

D68a: "Therapeutic Immunology" edited by K. Frank Austen et al., Chapter 24 "Monoclonal Antibodies to CD3", April 2001

D79: Choy et al., British. J. Rheumatol., 37: 484-490, (1998)

- X. Appellant I's arguments submitted in writing may be summarised as follows:

Main and auxiliary requests

Novelty

The sole data reported in document D4 assessing the suitability of F(ab')₂ fragments of anti-CD3 antibodies in the treatment of ongoing autoimmune diseases had been established in NOD mice. These mice were non-obese, had overt diabetes and served as a model for human autoimmune insulin-dependent diabetes. Other autoimmune diseases to be treated by these antibody fragments were simply listed, among them rheumatoid arthritis. The treatment of chronic joint inflammation as such by these fragments or in the context of rheumatoid arthritis was not disclosed.

- XI. Appellant II's arguments submitted in writing may be summarised as follows:

Main and auxiliary requests

Novelty

Document D4 disclosed the use of F(ab')₂ fragments of anti-CD3 antibodies for the treatment *inter alia* of

ongoing autoimmune diseases, in particular diabetes, rheumatoid arthritis, multiple sclerosis and psoriasis, through the induction of an antigen-specific unresponsiveness in T-cells, *i.e.* by immune tolerance.

The skilled person knew through common general knowledge that rheumatoid arthritis was characterised by chronic joint inflammation in which T-cells played a role.

It was established case law that a disclosure could anticipate claimed subject-matter only, if the teaching it contained was reproducible. Concerning the disclosure in a prior art document of a therapeutic effect, reproducibility in the context of novelty was assessed according to the same criteria as those that were used for sufficiency of disclosure, *i.e.* it had to be plausible to the skilled person that the therapeutic effect was achieved.

The experimental data disclosed in document D4 related to mice that were an accepted model for autoimmune insulin-dependent diabetes mellitus in humans. The results obtained with F(ab')₂ fragments of anti-CD3 antibodies in these mice made plausible a therapeutic effect in the treatment of chronic joint inflammation in rheumatoid arthritis, since all autoimmune diseases disclosed in document D4 as being suitable for the treatment with, *inter alia*, the anti-CD3 F(ab')₂ fragments were mediated by T-cells. Hence, the subject-matter of claim 1 of the main request and the auxiliary request was not novel over the disclosure in document D4.

XII. Appellant I requested in writing that the decision under appeal be set aside and that the patent be maintained as granted, or alternatively, on the basis of the auxiliary request.

Appellant II requested in writing that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. Both duly summoned appellants announced that they would not attend the oral proceedings. These took place in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

Introduction to the invention

2. The invention under consideration concerns the treatment of chronic joint inflammation, in particular in rheumatoid arthritis by the use of *inter alia* F(ab')₂ fragments from antibodies binding to the cluster of differentiation 3 (CD3) T-cell co-receptor on the surface of T-cells. In contrast to the complete antibodies, these fragments have lost the ability to activate T-cell proliferation accompanied by a release of inflammatory cytokines, since they are no longer able to bind to the Fc receptor on the surface of accessory cells. As a consequence the fragments have fewer adverse side-effects when administered to human patients (see paragraphs [0001], [0005], [0006], [0017] and [0018] of the patent).

Novelty (Article 54 EPC)

Main request - claim 1

3. It is established jurisprudence that the subject-matter of a claim lacks novelty if it is directly and unambiguously derivable from a prior art disclosure, either explicitly or implicitly (see Case Law of the Boards of Appeal, 7th edition, I.C.3.3).
4. Claim 1 relates, *inter alia*, to the use of F(ab')₂ fragments of anti-CD3 antibodies in the preparation of a medicament for the treatment of chronic joint inflammation.
5. Document D4 discloses the use of, *inter alia*, F(ab')₂ fragments of anti-CD3 antibodies for the treatment of, *inter alia*, "ongoing" rheumatoid arthritis (see claim 25 in combination with claim 16 and page 3, lines 12 to 14). The therapeutic effect is achieved by inducing immune tolerance in auto-reactive T-cells, *i.e.* in T-cells that are activated by endogenous antigens (see page 1, lines 11 to 18 and page 2, line 33 to page 3, line 5).
6. It is not disputed by the parties that in the present case the terms "ongoing" and "chronic" in relation to rheumatoid arthritis have the same meaning and that document D4 therefore discloses the treatment of chronic rheumatoid arthritis.
7. Appellant I, however, disputed that the treatment of rheumatoid arthritis disclosed in document D4 anticipated the treatment of chronic joint inflammation, since this document did not disclose the latter indication.

8. It was generally known to the skilled person before the priority date that chronic rheumatoid arthritis is characterised by a permanent inflammation of the joints. This is inferable, for example, from the term "arthritis" which literally means "joint(s) inflammation" or from document D79, which refers to rheumatoid arthritis as "*the most common inflammatory and destructive arthropathy*" that is "*characterized by a cell-mediated immune response in the synovial joints*" (see page 484, column 1, first paragraph, lines 2 and 3 and second paragraph, lines 1 and 2). Also, the background art part of the patent in suit discloses that "*rheumatoid arthritis is a chronic inflammatory disease affecting the joints*" (see paragraph [0002]).
9. It was also known from the prior art that a T-cell-mediated immune response was involved in the inflammation of the joints in the context of rheumatoid arthritis (see e.g. document D79, page 484, column 1, second paragraph to column 2, first paragraph and point 15.3 below).
10. In the board's view, the skilled person, knowing that the therapeutic effect of F(ab')₂ fragments of anti-CD3 antibodies in document D4 was due to inducing immune-tolerant T-cells (see point 5 above) and that auto-reactive T-cells are involved in the inflammatory processes of the joints (see point 9 above), would have derived from the disclosure of the treatment of chronic rheumatoid arthritis in document D4 the implicit disclosure of the treatment of chronic joint inflammation.
11. The board thus concludes that the skilled person would derive all the features of the subject-matter of claim 1

relating to F(ab')₂ fragments of anti-CD3 antibodies from the disclosure of document D4, explicitly and implicitly.

12. Appellant I further argued that document D4 could not be regarded as anticipating the subject-matter of claim 1, because it did not disclose experimental data showing a therapeutic effect of anti-CD3 antibody F(ab')₂ fragments in the treatment of rheumatoid arthritis. The disclosure of document D4 could therefore not be considered reproducible.
13. It is established case law that the disclosure content of a prior art document anticipates claimed subject-matter only if the teaching it contains is reproducible. The criteria for assessing a reproducible disclosure in the context of novelty (Article 54 EPC) and sufficiency of disclosure (Article 83 EPC) are the same.

A disclosure of a therapeutic use of a product is considered reproducible if it is at least plausible to the skilled person that the therapeutic effect at issue can be achieved. This is normally the case if evidence is available - either from the disclosure itself or from common general knowledge - that the product has, for example, a direct effect on the underlying metabolic mechanism specifically involved in the disease (see Case Law of the Boards of Appeal, 7th edition, I.C.3.11, last paragraph and e.g. decision T 609/02, point 9 of the reasons).

14. Hence, in view of the case law referred to in point 13 above, the absence of experimental data in a document relating specifically to the treatment of the disease under consideration does not inevitably mean that a

therapeutic effect is not plausible. For this reason alone, appellant I's argument is not convincing.

15. Moreover, an analysis of the experimental data of document D4 reveals the following:
 - 15.1 The document discloses a study which assesses the efficacy of anti-CD3 antibody F(ab')₂ fragments in the treatment of overt, *i.e.* established, diabetes in non-obese (NOD) mice (see example 1). The treatment achieves a remission of the diabetes in the animals treated (see page 6, table 1 and page 7, lines 1 to 3).
 - 15.2 At the priority date it was common general knowledge that NOD mice were an established model for human autoimmune insulin-dependent diabetes mellitus. It was moreover known that auto-reactive T-cells play a major role in this disease (see e.g. document D68a, page 337, column 1, fifth paragraph).
 - 15.3 The involvement of auto-reactive T-cells in the pathogenesis of rheumatoid arthritis was also known from the prior art. Document D79, for example, reads: "*Most researchers agree that RA [rheumatoid arthritis] is initiated by an antigenic or autoantigenic peptide complexed to the rheumatoid-associated major histocompatibility complex (MHC) class II molecules, HLA-DR4 or DR1, on the surface of an antigen presenting cell. This antigen-MHC complex is presented to CD4+ lymphocytes with the appropriate T-cell receptor, which become activated and increase their cell surface expression of many activation markers*" (see page 484, column 1, second paragraph to column 2, line 7; "CD4+" is a surface marker that is specifically expressed on T-cells; note and emphasis added by the board).

- 15.4 In the board's view therefore, it was part of the common general knowledge of the skilled person that both rheumatoid arthritis and insulin-dependent diabetes mellitus in humans are T-cell-mediated autoimmune diseases, *i.e.* that auto-reactive T-cells are the underlying mechanism involved in both diseases. Accordingly, in view of the results disclosed in document D4 in the treatment of insulin-dependent diabetes, the skilled person would have considered it plausible that the F(ab')₂ fragments of anti-CD3 antibodies would also achieve a beneficial effect in the treatment of rheumatoid arthritis.
16. In view of the above considerations, the board concludes that the disclosure of document D4 is to be considered reproducible.
17. Consequently, document D4 anticipates the subject-matter of claim 1. Hence, the main request does not fulfil the requirements of Article 54 EPC.

Auxiliary request - claim 1

18. The subject-matter of claim 1 differs from that of the main request in that it relates to "the treatment of chronic joint inflammation in rheumatoid arthritis".
19. The board has already established that chronic joint inflammation is characteristic of rheumatoid arthritis (see point 8 above). Therefore the reasons for finding that the subject-matter of claim 1 of the main request, *i.e.* the use of anti-CD3 antibody F(ab')₂ fragments in the preparation of a medicament for the treatment of

chronic joint inflammation, is not novel over the disclosure of document D4 apply *mutatis mutandis* to the auxiliary request. Thus, this request does not meet the requirements of Article 54 EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairwoman:



D. Hampe

G. Alt

Decision electronically authenticated