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Case Number: T 2637/11 - 3.3.04

Application Number: 02799751.9

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Language of the proceedings: EN

Title of invention:
Therapeutic monoclonal anti-TIRC7 antibodies for use in immune related and other diseases

Applicant:
CellAct Pharma GmbH

Headword:
Anti-TIRC7 monoclonal antibody/CELLACT

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step of all requests - (no)

Decisions cited:

Catchword:

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Case Number: T 2637/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 September 2015

Appellant: (Applicant)	CellAct Pharma GmbH Otto-Hahn-Strasse 15 44227 Dortmund (DE)
Representative:	Krauss, Jan Boehmert & Boehmert Anwaltspartnerschaft mbB Patentanwälte Rechtsanwälte Pettenkoferstrasse 20-22 80336 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 July 2011 refusing European patent application No. 02799751.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	M. Blasi

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application No. 02 799 751. This application was filed as an international application and published as WO 03/054019 (hereafter the "application") having the title "*Therapeutic anti-TIRC7 antibodies for use in immune related and other diseases*".

II. The examining division held *inter alia* that the subject-matter of claim 1 of the sole request before it lacked inventive step (Article 56 EPC) having regard to the disclosure of document D1 alone (the respective document is identified in section VI below).

III. The appellant indicated with its notice of appeal that its main request corresponded to the request on which the impugned decision was based, and filed with its statement of grounds of appeal three auxiliary requests.

Claim 1 of the main request reads:

"1. A monoclonal antibody or antigen binding molecule which is capable of binding to an antigen comprising or consisting of the amino acid sequence SEQ ID NO: 10 wherein the antibody or antigen binding molecule comprises the complementarity determining regions (CDRs) of the V_H and the complementarity determining regions (CDRs) of the V_L variable regions of which variable regions are set forth in Figure 6 (V_H) (SEQ ID NO: 6) and Figure 7 (V_L) (SEQ ID NO: 8)."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the words "comprising or" are deleted. Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that the expression "or antigen binding molecule" is deleted.

Claim 1 of auxiliary request 3 combines both amendments and thus reads:

"1. A monoclonal antibody which is capable of binding to an antigen consisting of the amino acid sequence SEQ ID NO: 10 wherein the antibody comprises the complementarity determining regions (CDRs) of the V_H and the complementarity determining regions (CDRs) of the V_L variable regions of which variable regions are set forth in Figure 6 (V_H) (SEQ ID NO: 6) and Figure 7 (V_L) (SEQ ID NO: 8)."

IV. Following a communication from the board pursuant to Article 15(1) RPBA setting out its preliminary view that the monoclonal antibodies referred to in claim 1 of all requests lacked unexpected properties vis-à-vis the polyclonal antibodies of document D1, the appellant submitted comparative experimental data of a monoclonal antibody according to claim 1, denoted as neliximab, and a polyclonal antibody of document D1 (the respective documents are identified in section VI below).

V. Oral proceedings before the board took place on 11 September 2015. During the oral proceedings the appellant referred to further experimental data submitted with its letter dated 20 July 2009 during the examination proceedings (the respective document is identified in section VI below). At the end of the oral

proceedings the chairwoman announced the board's decision.

VI. The following documents are cited in this decision:

D1: WO 99/11782

D2: Comparative experimental data filed with the letter dated 11 August 2015 concerning the effect of neliximab and a polyclonal anti-T-cell immune response cDNA 7 (TIRC7) antibody of document D1 on the expression of nuclear factor of activated T-cells, cytoplasmic (NFATc) and the phosphorylation of the protein 53 (p53).

D3: Experimental data of a study concerning neliximab's effect on allograft survival time in a mouse cardiac transplantation model submitted under the heading "*Efficacy in transplantation therapy*" with the letter dated 20 July 2009.

VII. The appellant's arguments may be summarised as follows:

The polyclonal anti-TIRC7 antibodies of document D1 represented the closest prior art. The antibodies of claim 1 differed therefrom by their monoclonal nature and in that amino acid sequences defining the specific complementarity determining regions (CDRs) were specified.

It was disclosed in the application that neliximab as an antibody representing the antibodies claimed inhibited T-cell proliferation including the secretion of interferon-gamma (IFN-γ) and interleukin-2 (IL-2) from these T-cells. This activity made it suitable for transplantation therapy.

The skilled person would infer from the claimed antibodies' usefulness for transplantation therapy as suggested in the application that this was due to the induction of immunotolerant T-cells. This effect was supported by the comparative data of document D2 that disclosed that neliximab increased the gene expression of the nuclear factor of activated T-cells, cytoplasmic (NFATc) - a central mediator known to be involved in the induction of immunotolerant T-cells - while the closest prior art polyclonal antibody Ab76 of document D1 had no effect on NFATc gene expression.

Document D3 disclosed that neliximab induced a long-term (145 days post-transplantation) heart allograft survival in 20% of the mice treated. A survival rate of 20% reflected a value associated with the presence of immunotolerant T-cells.

The induction of immunotolerant T-cells by neliximab improved its effectiveness in transplantation therapy vis-à-vis the closest prior art antibodies. The technical problem to be solved was thus the provision of immunosuppressive anti-TIRC7 antibodies that induced immunotolerant T-cells for improving transplantation therapy as reflected by an increased graft survival time.

Neliximab and the closest prior art antibodies were all raised against substantially identical epitopes on TIRC7 but surprisingly influenced immune signalling in T-cells differently. The antibodies according to claim 1 thus had superior properties which were unexpected and hence they involved an inventive step.

VIII. The appellant requested that the decision under appeal be set aside and that a European patent be granted on the basis of the set of claims of the main request on which the decision under appeal was based, or alternatively on the basis of one of the set of claims filed as auxiliary requests 1 to 3 with the statement of grounds of appeal.

Reasons for the Decision

Inventive step (Article 56 EPC)

Main request - claim 1

The invention

1. The invention concerns monoclonal antibodies directed against the extracellular domain of a T-cell immune response cDNA 7 (TIRC7) membrane protein that acts as a co-stimulatory molecule in the signal transduction process leading to T-cell activation and proliferation. Antibodies of the invention inhibit the proliferation as well as the secretion of interferon-gamma (IFN-γ) and interleukin-2 (IL-2) of T-cells (see example 1 and figure 3 of the application). The antibodies are thus capable of suppressing activated cells of the immune system which renders them potentially suitable for transplantation therapies (see page 1, lines 9 to 12 and page 4, lines 3 to 6 of the application).

Closest prior art

2. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal of the EPO generally apply the "problem and

solution approach", which requires as a first step the identification of the closest prior art (Case Law of the Boards of Appeal (CLBA), 7th edition 2013, I.D.2).

3. The board agrees with the examining division and the appellant that the disclosure of document D1 represents the closest prior art.

Document D1 discloses polyclonal antibodies against TIRC7 and refers in general to monoclonal anti-TIRC7 antibodies without disclosing their actual preparation (see page 4, second and third paragraphs; page 20, line 3). Three of the polyclonal antibodies are reported to inhibit T-cell proliferation and the T-cell-dependent secretion of IL-2 and IFN-γ (see page 50, second paragraph to page 51, first paragraph; page 52, first full paragraph). Thus, the document suggests that the anti-TIRC7 antibodies disclosed have an immunosuppressive potential which renders them suitable for preventing an undesired T-cell activation by a transplant (see page 4, last paragraph to page 5, first paragraph and page 18, lines 11 to 14). This potential of the antibodies is particularly confirmed by the achievement of a significant prolongation of the kidney allograft survival time in an *in vivo* animal model (see page 17, third paragraph; example 4; figure 7).

Two of the three immunosuppressive antibodies disclosed in document D1, denoted "Ab79" and "Ab76", were raised against two different but overlapping peptide epitopes on the extracellular domain of TIRC7 (see e.g. figure 2). These epitopes are designated "P6" (DLPDASVNGWSSDE; SEQ ID NO: 7) and "P2" (SSDEEKAGGLDDEE; SEQ ID NO: 4) (overlap underlined by the board).

In this context the board notes that the peptide epitope against which the antibody "neliximab", i.e. an antibody falling under the terms of claim 1, was raised (designated "7c": DLPDASVNGWSSDEEKAGGLDDEE, SEQ ID NO: 10; page 9, lines 11 and 12) consists in fact of the combined peptide epitopes "P2" and "P6" of document D1.

3.1 Consequently, the two polyclonal antibodies "Ab79" and "Ab76" of document D1 having an immunosuppressive activity on T-cells which renders them suitable for transplantation therapy and that bind to substantially identical epitopes on TIRC7 as the antibodies defined in claim 1 represent the closest prior art antibodies.

Problem to be solved and solution

4. The monoclonal antibodies according to claim 1 differ from each of the two closest prior art polyclonal antibodies by their monospecific binding to an epitope on TIRC7 and in that their complementarity determining regions (CDRs) have the amino acid sequences specified in the claim.

5. The appellant argued that the technical effect achieved by the claimed antibodies is that they have, in addition to an immunosuppressive activity - which the closest prior art antibodies also have - the ability to induce immunotolerant T-cells. This latter property further prolonged the survival time of allografts and thus improved the transplantation therapy based on the anti-TIRC7 antibodies of the invention.

6. This additional property of the antibodies was implied by the suggested use of the antibodies for transplantation therapy in the application (see e.g.

page 4, lines 29 to 33) and confirmed by the experiments disclosed in the post-published documents D2 and D3. In the appellant's view, the use of this effect for the formulation of the technical problem was thus allowable and accordingly considered as the provision of immunosuppressive anti-TIRC7 antibodies that induce immunotolerant T-cells for improving transplantation therapy.

7. Immunotolerant T-cells differ from immunosuppressed T-cells in that they no longer recognise an allograft as foreign antigen, i.e. if they are present permanent administration of immunosuppressive agents to prevent them from rejecting the graft is not required.

Immunosuppression of T-cells is characterised by a reduced activation and proliferation rate of alloreactive cells. This suppression does not necessarily result in the development of immunotolerance as evident from the life-long need of transplantation patients for immunosuppressive agents.

8. It has been established by the case law that only those technical effects that have actually been achieved in the light of the application can be taken into account for the formulation of the technical problem (CLBA, 7th edition 2013, I.D.4.3.2, last sentence; I.D.4.3.1, third paragraph). This criterion implies that the effects achieved must be derivable from the application (CLBA, 7th edition 2013, I.D.4.4.1, first paragraph). This also applies to cases concerning subsequently invoked technical effects. The case law in this matter has consistently held that effects which are not mentioned in the application may be considered when determining the technical problem to be solved only, when they can be deduced from the application (CLBA,

7th edition 2013, I.D.4.4.2, first paragraph, third sentence et seq.).

9. It has thus to be assessed in the present case whether it is derivable from the application that the antibodies claimed induce immunotolerant T-cells.

9.1 The application does not explicitly disclose that the claimed antibodies induce immunotolerant T-cells.

9.2 As to an implicit disclosure, the application only suggests the use of the anti-TRC7 antibodies claimed for transplantation therapy because they prevent graft rejection (see for example page 4, lines 4 to 5 and lines 30 to 33).

9.3 Regarding the mechanism underlying this effect, the examples of the application do not point to the induction of immunotolerance. In the context of example 1 it is disclosed that an antibody falling under the terms of claim 1, denoted as neliximab, inhibits under *in vitro* conditions the proliferation of mitogen-stimulated peripheral blood mononuclear cells (PBMCs) - a cell preparation including T-cells - as well as the secretion of IL-2 and IFN-γ from these cells (see example 1, page 25, lines 9 to 12 and 25 in combination with figure 3).

Based on his or her common general knowledge the skilled person would have interpreted these results to mean that the monoclonal anti-TIRC7 antibodies of the invention have, like the polyclonal antibodies of document D1 (see point 3 above), an immunosuppressive effect on T-cells by inhibiting their activation and proliferation, but not that they induce immunotolerance.

9.4 Also, it is not derivable from any of the available prior art documents that TIRC7 signalling mediates immunotolerance, or that anti-TIRC7 antibodies induce such an immunotolerance. Nor is it derivable from any of these documents that immunotolerance is necessarily involved in, or that it is even the only mechanism which prevents graft rejection. Document D1, for example, discloses immunosuppression, i.e. suppression of T-cell proliferation and activation by interfering with the secretion of IL-2 and IFN-γ as the sole mechanism of action of polyclonal anti-TIRC7 antibodies which prevents allograft rejection (see point 3 above). Thus, also the common general knowledge would not have prompted the skilled person to infer from the suggested use of the antibodies claimed for transplantation therapy that this is based, at least in part, on the antibodies' ability to induce immunotolerance.

10. Therefore, the board concludes that it is not derivable from the application that the claimed antibodies induce immunotolerant T-cells and this effect cannot accordingly be relied on for the formulation of the technical problem (see point 8 above).

11. In the board's view, the conclusion that the induction of immunotolerance is not derivable from the application is also supported by the appellant's submission in the context of assessing the obviousness of the subject-matter claimed. The appellant argued that it was surprising in view of the evidence from the post-published documents D2 and D3 that the monoclonal antibody neliximab influenced immune signalling in T-cells differently than the polyclonal antibody Ab76 disclosed in document D1, although both antibodies recognised a substantially identical epitope on TIRC7.

12. It also follows from the board's conclusion in point 10 above that the evidence in the post-published documents D2 and D3 that the antibodies claimed in fact have the desired property cannot be taken into account (see point 8 above).

13. Regarding documents D2 and D3 it is noted that even if they were taken into account, the board is not convinced that the data in these two documents support an improved transplantation therapy by the antibodies claimed (as represented by the neliximab antibody in these documents) vis-à-vis the closest prior art antibodies.

In fact, document D2 compares the effects of neliximab with only one of the two polyclonal antibodies of document D1, and on the expression of nuclear factor of activated T-cells, cytoplasmic (NFATc) for which there is no evidence available that it plays a role in the process of inducing immunotolerance. Document D3 compares neliximab's effect on the allograft survival time with that of cyclosporin A, i.e. an agent that is structurally and functionally unrelated to anti-TIRC7 antibodies.

14. The board therefore considers that, since a particular technical effect of the antibodies of the invention vis-à-vis the closest prior art antibodies is not apparent, the technical problem to be solved is the provision of alternative immunosuppressive anti-TIRC7 antibodies suitable for transplantation therapy.

15. The board is satisfied that this technical problem is solved in view of the evidence disclosed in the application (see point 9.3 above).

Obviousness

16. The question to be assessed here is whether or not the skilled person, starting from the antibodies A76 and A79 disclosed in document D1 and faced with the problem defined in point 14 above, would be motivated to provide the claimed antibodies as alternatives.

17. Document D1, in view of the beneficial therapeutic effect of the antibodies disclosed, suggests that "*the striking capacity of anti-TIRC7 antibodies to significantly prolong allograft survival in vivo provides an attractive approach to inhibit T-cell activation in human organ transplantation and autoimmune diseases*" (see page 18, first paragraph). The board considers this sentence to reflect the motivation for the skilled person to seek for alternative immunosuppressive anti-TIRC7 antibodies suitable for transplantation therapy.

18. As outlined in point 3 above, document D1 not only discloses polyclonal antibodies directed against defined epitopes of the extracellular domain of TIRC7 but also generally refers to monoclonal anti-TIRC7 antibodies and the hybridoma technology for their preparation (see page 15, lines 18 to 27, page 20, lines 1 to 9).

19. In the board's judgement, the skilled person would thus derive from the teaching of document D1 that monoclonal anti-TIRC7 antibodies will be useful for transplantation therapy. Its teaching moreover provides all the relevant technical instructions for the preparation of such antibodies by the use of standard hybridoma technology, in particular the sequences of antigens allowing the raising and selection of such

antibodies (see point 3 above). In this context it is again emphasised that the sequence of the antigen to which the claimed antibodies bind is in fact a combination of the antigens against which the two closest prior art antibodies A76 and A79 are raised.

20. Therefore the skilled person applying the teaching of document D1 would arrive at the provision of antibodies according to claim 1 in an obvious manner. Consequently, the subject-matter of claim 1 cannot be considered to involve an inventive step and the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary requests 1 to 3 - claim 1

21. Claim 1 of the main request is directed to a "monoclonal antibody or antigen binding molecule which is capable of binding to an antigen comprising or consisting of the amino acid sequence SEQ ID NO: 10 [...]" (see section III above). The subject-matter of claim 1 of auxiliary requests 1 to 3 differs therefrom by the deletion of the embodiment "antigen binding molecule" (auxiliary requests 2 and 3) and/or by the deletion of the embodiment "comprising" in the definition of the antigen (auxiliary requests 1 and 3).

22. The board's reasoning with regard to claim 1 of the main request applies *mutatis mutandis* to these amended claims because it concerns firstly the monoclonal antibody-embodiment of the claim and not that of the antigen binding molecule. Secondly, there is no reason to assume that the skilled person following the teaching in document D1 and arriving at antibodies that bind to an antigen comprising the amino acid sequence

SEQ ID NO: 10 would not also arrive at those binding to an antigen consisting of this amino acid sequence. This is so because the skilled would raise antibodies against the antigens specified by the sequences designated either "P6" or "P2" which both are fully comprised by the amino acid sequence defined as SEQ ID NO: 10 (see point 3 above).

23. Hence, the board arrives at the conclusion that none of the three auxiliary requests fulfils 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