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Datasheet for the decision of 16 February 2021

Case Number: T 0941/16 - 3.3.08

Application Number: 11151622.5

Publication Number: 2363486

IPC: C12N15/13, A61K47/48, C07K16/30

Language of the proceedings: EN

Title of invention:
Monoclonal antibodies and single chain antibody fragments against cell-surface prostate specific membrane antigen

Applicant:
Universitätsklinikum Freiburg

Headword:
anti-PSMA antibody/UNIVERSITÄTSKLINIKUM FREIBURG

Relevant legal provisions:
EPC Art. 83, 116(1)

Keyword:
Sufficiency of disclosure of all claim requests - (no)
Request for further oral proceedings (dismissed)

Decisions cited:
G 0001/03, T 0547/88, T 0692/90, T 0748/91, T 0025/91, T 0731/93, T 0194/96, T 0298/97, T 0617/07, T 1775/12

Catchword:

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Case Number: T 0941/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 16 February 2021

Appellant: (Applicant)	Universitätsklinikum Freiburg Hugstetter Strasse 49 79106 Freiburg (DE)
Representative:	Keller, Günter Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstrasse 2 80538 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 13 October 2015 refusing European patent application No. 11151622.5 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. Montrone
	R. Winkelhofer

Summary of Facts and Submissions

I. This appeal is against the decision of an examining division to refuse the European patent application No. 11 151 622.5, published as EP 2 363 486 ("patent application"). It is a divisional application of the earlier European patent application No. 06 707 388.2, which was filed under the PCT and published as International patent application WO 2006/125481.

II. The examining division held in the decision under appeal that the subject-matter of claims 1 of the main request and of auxiliary requests 1 to 3 lacked an inventive step (Article 56 EPC).

III. With the statement of grounds of appeal, the applicant (hereinafter "appellant") submitted a main request and three auxiliary requests which are identical to the respective sets of claims dealt with in the decision under appeal. In addition, documents D16 to D25 were submitted.

IV. In a communication pursuant to Article 15(1) RPBA, the appellant was informed of the board's provisional, non-binding opinion. The board raised new objections of lack of clarity and insufficiency of disclosure against the subject-matter of claims 1 of all claim requests on file, and introduced additional prior art.

V. In reply, the appellant filed arguments, further documents and experimental data (documents D29 to D31).

VI. Oral proceedings before the board were held on 3 September 2020. After hearing the appellant on issues of Articles 84, 83 and 56 EPC, the debate was closed

and the proceedings continued in writing, to provide the appellant with a further opportunity to submit documentary and experimental evidence in support of their case on Article 83 EPC. *Inter alia* the appellant was asked to submit evidence in support of their statement that any three CDRs were sufficient to determine the binding specificity of an antibody, and that the CDR3 of the light and/or heavy variable chain of the claimed monoclonal antibody/fragment could be modified without distorting it's binding properties.

VII. The appellant in a further submission filed additional documents and experimental data (documents D32 to D38).

VIII. Claim 1 of the main request reads:

"1. An isolated monoclonal antibody or an antigen binding portion thereof which

a) binds to prostate specific membrane antigen in its native form occurring on the surface of tumor cells

b) can be internalized by a tumor cell,

c) binds strongly to LNCAP cells but not or only minimally to cells which lack expression of prostate specific membrane antigen and

d) is linked to a label or a cytotoxic agent, characterized in that

e1) it comprises at least three of the CDR sequences selected from the group consisting of the CDRs designated as CDR H1, H2, H3, L1, L2 and L3 as shown in Fig. 21 or

e2) it comprises at least three of the CDR sequences selected from the group consisting of the CDRs designated as CDR H1, H2, H3, L1, L2 and L3 as shown in Figure 20."

IX. Claim 1 of auxiliary request 1 differs from claim 1 of of the main request, in that feature e2) has been deleted.

X. Claim 1 of auxiliary request 2 differs from claim 1 of of the main request, in that in features e1) and e2) the term "at least three of the CDR sequences" has been replaced by the term "at least five of the CDR sequences".

XI. Claim 1 of auxiliary request 3 differs from claim 1 of of the main request, in that in feature e1) the term "at least three of the CDR sequences" has been replaced by the term "at least five of the CDR sequences", and in that feature e2) has been deleted.

XII. The following documents are referred to in this decision:

D17: "Experimental report concerning the binding properties of constructs wherein the sequence of one CDR is slightly changed", First experimental report on humanisation of the "D7" scFv, submitted 18 February 2016;

D18: "2. Humanisierungsversuch", Second experimental report on humanisation of the "D7" scFv, submitted 18 February 2016;

D19a: "3. Humanisierungsversuch", Third experimental report on humanisation of the "D7" scFv,

submitted 18 February 2016;

D19b: "Specific binding of the humanized scFv variants of the anti-PSMA scFv D7",Fourth experimental report on humanisation of the "D7" scFv; submitted 16 February 2016;

D29: L. Riechmann and S. Muyldermans, Journal of Immunological Methods, 1999, Vol. 231, 25-38;

D30: Z. Liu *et al.*, Journal of Molecular Recognition, 1999, Vol. 12, 103-111;

D31A: "Sequences of humanised VH and VL chains", submitted 27 January 2020;

D31B: Experimental data on "Cell binding of humanised anti-PSMA antibodies", submitted 27 January 2020;

D32: Antibody Engineering, R. Kontermann and S. Dübel (Eds.), 2001, Springer, 549-552;

D33: L.S. Jespers *et al.*, BIO/TECHNOLOGY, 1994, Vol. 12, 899-903;

D34: C. Rader *et al.*, PNAS, 1998, Vol. 95, 8910-8915;

D35: Recombinant Antibodies, S. Dübel and F. Breitling (Eds.), 1999, John Wiley & Sons, Inc. and Spektrum Akademischer Verlag, 54-59;

D36: R.-M. Lu *et al.*, Journal of Biomedical Science, 2020, Vol. 27(1), 1-30;

D37: "Humanization of the anti-PSMA mAh 3/F11", Experimental report on the humanisation of the

anti-PSMA mAb 3/F11 of Prof. Dr. P. Wolf, dated 15 October 2020;

D38: EP1516275 (published 7 March 2007).

XIII. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request

Sufficiency of disclosure

The patent application did not contain any experimental data about antibodies with the structural and functional features of claim 1. However, it disclosed the need for generating humanising murine antibodies (see paragraph [0029] of the application).

In line with the decision T 617/07, in order to assess sufficiency of disclosure of an application, the knowledge of the skilled person had to be taken into account. At the priority date of the patent application, the skilled person was familiar with antibody constructs containing only three complementarity-determining regions (CDRs) that bound to antigens, for example, camelised antibodies (see document D29). It was known that single mutations in CDRs of humanised antibodies resulted in the reduction or even the complete loss of the antibody's binding activity. However, such mutations were performed only with a mind to maintain the advantageous properties of the murine antibody. Moreover, mutational approaches were available at the filing date of the patent application that allowed the identification of positions within the CDR which could be modified, except for proline, without distorting the antibody's

binding properties (see e.g. document D30, pages 107 and 108, Figure 3). Various methods for humanising antibodies were available at the filing date of the patent application, including guided selection, selection from phage libraries, or chain shuffling. These methods allowed the isolation of humanised antibodies having up to three slightly modified CDRs which still bound to the same epitope as the parental murine antibody. Even examples of antibodies were known where it was sufficient that only one of the six murine CDRs was retained (see documents D32, page 551, Figure 1 and page 552, first paragraph; document D33, Figure 1, page 899, column 1, second paragraph from the bottom; document D34, Figure 1, page 8912; document D35, sections 2.4.5.).

Furthermore, various experimental reports of humanised antibodies were submitted to provide evidence that the skilled person was able to obtain the claimed antibodies/fragments by using standard methods known in the art. Documents D17, D18, D19a and D19b disclosed experimental evidence that humanised scFv antibodies derived from the sequences disclosed in Figure 21 of the patent application (i.e. the murine "D7" antibody) showed the binding properties of the parental antibody. Although claim 1 defined no order for the CDRs, the skilled person would have used them in the humanisation process in their corresponding order. Further examples of D7-derived humanised antibodies were shown in document D31 (see Figures D31A to D31C), and in document D37. All of these data provided evidence that by using standard methods in the art the skilled person was able to obtain humanised antibodies with one to three slightly mutated CDRs compared to the murine D7 antibody that showed the functional properties defined

in claim 1. Furthermore, these properties were easily determined by routine methods.

Biochemical inventions should not be treated worse than inventions in the field of classical chemistry. In the latter field it was common to receive a granted patent claiming compounds defined by a broad chemical formula encompassing millions of compounds, even if only one or a few compounds were disclosed in the patent application showing a desired property. The presence of non-working embodiments in such formula did not result in the invalidation of the claimed subject-matter.

XIV. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the main request or auxiliary requests 1 to 3, all submitted on 18 September 2015. The appellant requests further (new) oral proceedings.

Reasons for the Decision

Procedural issues

1. It should be noted that despite the appellant's request in their submission of 16 October 2020 for further (new) oral proceedings, the appeal proceedings could be terminated in writing, without appointing such further oral proceedings.

2. Pursuant to Article 116(1) EPC, a request for further oral proceedings may be rejected if the parties and the subject of the proceedings are the same.

3. According to the case law of the Boards of Appeal, the subject of the proceedings is the same if no substantially new situation has arisen after the first

oral proceedings that could justify renewed oral proceedings (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019 (hereinafter "Case Law") III.C.4.4; T 25/91, point 3.2 of the Reasons; T 1775/12, points 4 ff of the Reasons, with in-depth considerations including an analysis of the travaux préparatoires to Article 116 EPC).

4. In particular, the subject of the proceedings remains the same if their continuation in writing after the first oral proceedings was merely to provide further clarification of the facts as discussed in the oral proceedings (see T 692/90, point 6 of the Reasons; T 547/88, point 2 of the Reasons; T 748/91, point 6 of the Reasons; T 298/97, OJ 2002, 83, point 13 of the Reasons). The situation would be different if new documents were submitted after the first oral proceedings, which are more pertinent than the documents on file, and which could or did radically change the nature of the decision to come (see T 194/96, point 3 of the Reasons). Likewise, the subject of the proceedings could change, if the issuing of a reasoned decision depended on the submission of new evidence (cf T 731/93, point 4 of the Reasons). However, the mere submission of new documentary or experimental evidence cannot be decisive for answering the question whether or not the subject of the proceedings has changed. It rather depends on the specific facts of the case, since otherwise the submission of new evidence would make the holding of further oral proceedings mandatory.

5. In the present case, the debate had been closed at the end of the (first) oral proceedings. The case might have been decided then. However, it seemed fair to give the appellant a further opportunity to submit evidence

to support their arguments atop the evidence already discussed in the oral proceedings in view of the questions at stake, in particular under Article 83 EPC. Accordingly, it was decided that the proceedings were to be continued in writing. In this context, the board does not concur with the appellant that the objections raised were overcome in principle. On the contrary, if this were the case, there would have been no need for the appellant to submit additional evidence. As indicated above, it was considered a matter of fairness to give the appellant another opportunity to back up their statements made at the oral proceedings, and not to create a fresh (new) case that would have merited further discussions.

6. The appellant has now submitted such evidence (documents D32 to D38) in support of their position that the invention was, in fact, sufficiently disclosed (Article 83 EPC). To be laid out below, this documentary and experimental evidence neither alters the conclusions on Article 83 EPC, nor do they introduce a substantially new case that would call for a renewed exchange with the appellant in writing or even in new oral proceedings. They do not go beyond the case as defined by the appellant's requests at the outset of the appeal proceedings, and the relevant issues at stake as framed by the board’s first communication of 2 January 2020, and the discussions in the oral proceedings of 3 September 2020. Further to be shown below, the evaluation of this evidence does not leave the framework of the previous proceedings, nor does it require further oral discussions or such in writing.

7. Since an opportunity for filing further evidence in support of arguments made at the first oral proceedings

before the board has been given to the appellant, and no issues requiring further proceedings, either written or oral, have resulted therefrom, the request for a second oral proceedings could not be granted.

Main request and auxiliary request 1

Claim construction - claim 1

8. Claim 1 is directed to an isolated monoclonal antibody or an antigen binding portion thereof (hereinafter "antibody/fragment"). The antibody/fragment is characterised by the functional properties of (i) binding to native surface-bound prostate specific membrane antigen (PSMA) on tumour cells, (ii) an ability to become internalised, and (iii) a strong binding to LNCaP cells with either no or a minimal binding to cells devoid of PSMA expression.

8.1 The meaning of "*strongly*" and "*minimally*" binding of the antibody/fragment in item c) of claim 1 is relative. This property is solely assessed in relation to LNCaP cells without indicating a reference antibody or affinity values/ranges as determined by a specified reference method. The term "*minimally*" implies that an antibody/fragment showing a certain cross-reactivity to antigens different from PSMA likewise falls within the claimed ambit.

8.2 The claimed antibody/fragment is further structurally defined by the presence of (iv) labels or cytotoxic agents of any type, and (v) by having "*at least three*" complementarity-determining regions (CDRs) selected from a group of six CDR sequences. The variable heavy chain (V_H) and the variable light chain (V_L) of an antibody contain each three CDR sequences, i.e. "*CDR*

H1, H2, H3", and "*CDR L1, L2 and L3*" respectively. The sequence information for the CDRs referred to in claim 1 can be derived from the two murine single chain variable fragments (scFv) shown in Figures 20 or 21 (claim 1 of the main request), or in Figure 21 only (claim 1 of auxiliary request 1). These scFvs are designated in the patent application as "*H12*" and "*D7*", respectively (see e.g. paragraph [0045]).

8.3 Since nothing more than the selection of at least three CDRs from the group of six is required, claim 1 encompasses any anti-PSMA antibody/fragment with **only three** CDRs arbitrarily selected from the group of six CDRs of the variable heavy and/or light chain domains disclosed in either Figures 20 or 21 and three further unrelated CDRs. In other words, there is no requirement in claim 1 that all three CDRs from a single variable chain are present in the claimed antibody/fragment, nor that the specific CDR H3 and/or CDR L3 sequences are present.

Sufficiency of disclosure - claim 1

9. In the jurisprudence regarding Article 83 EPC it has been established that the claimed invention must be sufficiently disclosed on the relevant date of the application (see Case Law, II.C.2.), based on the application as a whole (*ibid.*, II.C.3.1), in consideration of the common general knowledge of the skilled person (*ibid.*, II.C.4.). At least one way of carrying out the claimed invention must be disclosed, but this disclosure is sufficient only if it allows the invention to be performed in the whole range claimed (*ibid.*, II.C.5.2., II.C.5.4 and II.C.7.1.2). Furthermore, the disclosure must be reproducible without undue burden. Where the person skilled in the

art has to find out by trial and error which compound, if any, meets the parameter set out in the claim, this constitutes an undue burden, even if it involves routine experimentation (*ibid.*, II.C.6.7.).

10. Claims 1 of the main request and of auxiliary request 1 encompass both as an embodiment an antibody/fragment that contains **three** CDRs **only** selected from a group of six CDRs derived from the heavy and/or light variable chains of the scFv construct disclosed in Figure 21 and three further unrelated CDRs. Such an antibody/fragment has to be able to become internalised, and is required to bind "*strongly*" to native PSMA on LNCaP cells while showing either a minimal or no cross-reactivity with cells not expressing PSMA. There is no requirement in claim 1 that the three CDRs are all derived from one of the two variable chains only, nor that the CDR H3 and/or CDR L3 sequences are present. This embodiment of claim 1 will be assessed in the following.

11. In determining whether or not the disclosure is sufficient, it has to be assessed whether the patent application provides the skilled person taking their common general knowledge into account, with all the information necessary for carrying out the claimed invention (here the provision of any antibody/fragment comprising three CDRs derived from the heavy and/or light chains of the specific scFv construct disclosed in Figure 21 with the functional properties defined in claim 1).

12. The patent application suggests in general the use of humanisation protocols for generating a claimed antibody/fragment. In this context the patent application states: "*In order to maintain the preferred binding properties the sequences of the CDRs should be*

maintained as far as possible. It may be required, however, to perform some amino acid changes in order to optimise the binding properties. This can be performed by the person skilled in the art by standard proceedings. Furthermore by introducing a human framework it may be necessary to perform amino acid changes and/or deletions in order to improve the properties of the construct" (see paragraph [0029], lines 36 to 40). Sequence information about the CDRs of the parental murine D7 scFv construct to be used as "starting material" for a humanisation is disclosed in Figure 21. However, the patent application is silent on any specific humanisation protocol, nor are mutational approaches mentioned for optimising the binding properties of the antibodies/fragments obtained. The patent application is also silent on exemplary humanised antibodies/fragments showing the functional properties defined in claim 1.

13. In the absence of examples or a concrete technical guidance in the patent application for obtaining a claimed antibody/fragment, the issue is whether it is plausible, based on the evidence on file and taking common general knowledge into account, that a skilled person starting from the sequences of the murine scFv construct disclosed in Figure 21 of the patent application, and taking any arbitrary combination of three CDRs thereof in combination with three other structurally unrelated CDRs, will necessarily and reliably obtain antibodies showing the functional properties as defined in claim 1 by investing a reasonable amount of trial and error only. In other words, whether a claimed antibody/fragment can be obtained over the whole breadth of claim 1 without undue burden (see board's communication dated 2 January 2020, point 20).

14. The appellant argued that any combination of three CDRs of a murine antibody was sufficient to obtain humanised variants thereof binding to the same epitope on an antigen as the murine antibody, i.e. with a preserved binding specificity. It was uncontested that minor changes in a single CDR could substantially reduce or even abolish the binding of an antibody to its epitope, i.e. its binding affinity or strength. Consequently, the amino acid sequences of the murine CDRs are critical for the functional properties of the antibody/ fragment under consideration.

15. As regards the common general knowledge that the combination of any three murine CDRs is sufficient to obtain humanised antibodies with the same binding specificity and affinity, the appellant submitted various documents.

15.1 Document D29 discloses that a "*camelised*" single human V_H domain, i.e. an antigen-binding construct containing three CDRs from a single domain of a variable heavy chain only, may bind to an antigen (see document D29, abstract). While single domain antibodies were known at the relevant date of the patent application, claim 1 is not limited to such antibodies but comprises, for example, as in the embodiment under consideration, a complete monoclonal antibody that contains six CDRs (see board's communication dated 2 January 2020, point 7.1). Furthermore, as set out above, there is no requirement in claim 1, contrary to the camelised antibody in document D29, that all three CDRs are derived from a single variable domain, nor that the CDR3 of either the heavy or light chain is present. Accordingly, document D29 fails to support the appellant's case.

15.2 Further documents concern the humanisation of mouse monoclonal antibodies by various methods, including "*Guided Selection*" or "*chain shuffling*" (see document D32, title; document D33, abstract; document D35, page 54, third paragraph), or by phage display (see document D34, abstract).

15.3 These documents disclose that antibodies obtained by guided selection or chain shuffling are fully human, i.e. do not contain mouse-derived CDR sequences. Fully human antibodies do not fall within the scope of claim 1, and hence, are not relevant for the embodiment under consideration (see documents D32 and D33, Figure 1; document D35, page 54, third paragraph, Figure 2.17). Moreover, the binding specificity of these fully human antibodies "*most likely*" differs from the murine antibody (see document D33, page 902, column 1, first full paragraph), or "*may lead to the production of a humanized antibody that recognizes a slightly different epitope*" (see document D34, page 8914, column 2, fourth paragraph).

15.4 Documents D32 and D34 disclose further that for humanised antibodies containing murine CDR sequences the presence of the murine "*HCDR3*" (CDR H3) or the "*CDR3's in both heavy and light chain*" (i.e. both, CDR H3 and CDR L3) are necessary to retain the murine antibody's binding specificity (see document D32, page 552, first paragraph; document D34, abstract). Document D32 states in this context: "*Recently, we succeeded in humanising antibodies, which had the same epitope specificity as the original murine antibodies, by retaining the murine HCDR3 (Klimka et al., 2000; Beiboer et al., 2000). Rader et al. humanised the murine antibody (directed to human integrin $\alpha_v\beta_3$) by*

guided selection but succeeded only by retaining the murine CDR3's in both heavy and light chain (Rader et al., 1998)" (see page 552, first paragraph, emphasis added).

15.5 The "*Rader et al.*" document cited in document D32 above is document D34 in these proceedings, and reports the following: "*An entirely selective humanization strategy based on phage display libraries has been reported by Jespers et al. (31)* (i.e. document D33 in the proceedings, comment added by the board). *[...]. Though this strategy may compete with CDR grafting because the arduous fine-tuning steps are unnecessary, the lack of other successful applications of this approach - and our failed attempts to humanize LM609 by this approach for comparative studies — suggest that in contrast to CDR grafting, the general applicability of this approach for antibody humanization is uncertain. Also, since this approach is a sequential chain shuffling procedure, it may lead to the production of a humanized antibody that recognizes a slightly different epitope (32-34). It has been observed that antibodies consisting of the same heavy chain paired with light chains that differ in LCDR3 and elsewhere in V_L may bind different epitopes on the same antigen*" (see page 8914, column 2, fourth paragraph, emphasis added). Document D34 further states: "*By preserving the original LCDR3 and HCDR3 sequences of LM609 while subjecting the remaining sequence to selection, our humanization strategy was designed to ensure antigen specificity and epitope conservation. LCDR3 and HCDR3 contain the hypervariable joints of the V/J and V/D/J gene rearrangements that participate in direct antigen contact in all studied antigen/ antibody complexes (37). Unlike the other CDR regions, both LCDR3 and HCDR3 interact with all three CDRs of the other*

variable domain (38). Thus, although generalizations might be misleading (37), LCDR3 and HCDR3 can be considered to make the most significant contributions to affinity and specificity" (see page 8915, column 1, second paragraph, emphasis added).

15.6 Thus, it is derivable from the prior art documents D32 to D35 that retaining the murine CDR H3 or CDR L3 alone, even if starting from the entire light or heavy chain (containing all thee CDRs from one variable domain), may fail to reliably obtain humanised antibodies characterised by the same binding specificity and/or affinity as the mouse antibodies.

16. Further in support of their case, the appellant submitted several experimental reports on the humanisation of the murine scFv D7 antibody to demonstrate, that the skilled person using standard methods available at the relevant date of the patent application would have obtained an antibody/fragment according to claim 1.

16.1 Document D17 discloses two humanised antibodies which have in their CDR H2 region two amino acids replaced compared to the murine D7 antibody (see D17, page 1, last paragraph and Figure 1). These changes have not "*substantially changed specificity of the PSMA binding*", i.e. the binding to the same epitope on PSMA compared to the murine D7 antibody (see document D7, page 5, last paragraph, document D18, page 1, last but one paragraph to page 2, first paragraph).

16.2 Document D19a discloses 16 further humanised D7-derived antibodies wherein in the variable heavy chains one CDR (CDR H2) has been modified, while in the variable light chains either one (CDR L1) or two CDRs (CDR L1 and CDR

L2) have been modified, compared to the murine D7 antibody (see page 1, Figure 1 and page 2, Figure 2). The binding specificity to native PSMA of the humanised antibodies and the murine D7 antibody is similar (see document D19a, Figures 3 to 5; and document D24, Figure 1 and page 3, first paragraph), while the binding affinity of the humanised antibodies compared to the murine antibody can be similar or significantly lower (see document D19b, Table 2).

16.3 Document D31b discloses that substitutions of amino acids in CDRs have a strong impact on the humanised antibodies' binding affinity, including a strong reduction.

16.4 Document D37 discloses further humanised D7 antibodies obtained by three different methods: (i) "*Germline-optimized CDR grafting*" (see page 1, point 1), (ii) the use of "*the Epibase® platform*" (see page 3, point 2), and (iii) by "*in silico modelling*" (see page 5, point 3). Humanised antibodies generated by the first method differ from the murine antibody in CDR H1 and CDR H2 (see Figures 1B and 1D, in conjunction with Tables 1 and 2), or in CDR H2, CDR L1 and CDR L2 (see Figure 1C, in conjunction with Tables 1 and 2). The humanised antibodies show in comparison an improved, equal or lower binding to PSMA cells (see Figures 1A to 1D). Humanised antibodies generated by the second and third method show a similar binding specificity to PSMA compared to the murine antibody (see Figures 2 to 4).

17. In summary, the various humanised antibodies disclosed in documents D17 to D19a/b, D31b and D37 have retained the binding specificity of the murine D7 antibody, despite up to three CDRs having been slightly modified. However, the binding affinity of these humanised

antibodies varies, and may even be lower than that of the murine antibody. None of the humanised antibodies shows a modification in the CDR L3 and/or CDR H3 sequences. In other words, the presence of unmodified murine CDR H3 and CDR L3 in these humanised antibodies seems to be essential for retaining the functional properties defined in claim 1.

18. CDR H3 and CDR L3s' impact on an antibody's binding specificity and affinity was discussed with the appellant during the oral proceedings, because these two CDRs often play a dominant role (see point 15.5). However, as set out above, their presence is not required in the claimed antibody/fragment, although the experimental data in documents D17 to D19a/b, D31b and D37 disclose that antibodies with the functional properties defined in claim 1 all contain murine CDR H3 and CDR L3. The appellant was therefore asked at the end of the oral proceedings to provide further data demonstrating that an antibody/fragment as claimed was obtainable by modifying the CDR H3 and/or CDR L3. Such data have not been submitted.

19. Consequently, the common general knowledge together with the experimental data set out above, cannot support the appellant's assertion that selection of any three murine CDRs was sufficient to obtain humanised antibodies/fragments retaining the functional properties indicated in claim 1. Based on the evidence on file, rather the presence of both murine CDR H3 and CDR L3, and not only one or none, seems to be necessary to reliably obtain a claimed antibody/fragment.

20. In these circumstances, in the absence of any examples of a claimed antibody/fragment, except for the murine D7 and H12 scFv antibodies of Figures 20 and 21

comprising **all six CDRs**, the general information in the patent application and the common general knowledge taken together, cannot be considered to provide the information necessary to allow the skilled person to reliably obtain substantially all of the claimed antibodies/fragments fulfilling the functional requirements of the claim. For particular combinations of CDRs (lacking an unmodified CDR H3 and CDR L3) it is not credible that a humanised antibody/fragment with the properties defined in claim 1 will be obtained. Readily performing the invention across the entire scope of the claim places an undue burden onto the skilled person.

21. The appellant further referred to decision T 617/07. Without going into the details of the facts underlying this case, it is evident that experimental evidence of a humanised antibody with a modified CDR H3 sequence was available which retained the claimed functional properties (see points 29 and 30 of the Reasons). As set out above, no such evidence is available for an antibody/fragment according to claim 1.

22. Lastly, the appellant has submitted that patent applications in the field of biochemistry should not be treated worse than in the other fields of classical chemistry, where the presence of non-working embodiments in a generic chemical formula did not result in the invalidation of the claimed subject-matter. According to the case law (see point 9 above), the requirements of sufficiency of disclosure apply to all technical fields. Thus, depending on the individual case, inventions relating to a generic chemical formula comprising non-working embodiments with functional features contravene the requirements of Article 83 EPC

too (see G 01/03, OJ 2004, 413, point 2.5.2 of the Reasons).

23. To conclude from the above, the requirements of Article 83 EPC are not complied with.

Auxiliary requests 2 and 3

24. Claim 1 of auxiliary request 2 differs from claim 1 of of the main request, in that in features e1) and e2) the term "*at least three of the CDR sequences*" has been replaced by the term "*at least five of the CDR sequences*".

25. Claim 1 of auxiliary request 3 differs from claim 1 of of auxiliary request 2, in that feature e2) has been deleted.

26. Claims 1 of auxiliary requests 2 and 3 comprise both as an embodiment an antibody/fragment that is structurally characterised in that it comprises at least five of the murine CDRs shown in Figure 21 of the patent application. This necessarily implies that one of the CDR H3 or CDR L3 is contained in the claimed antibody/ fragment, while the second CDR3 can be present or absent. In other words, claim 1 encompasses as an embodiment an antibody/fragment which comprises only one of CDR H3 or CDR L3. This embodiment will be considered in the following.

27. Since the embodiment under consideration does not comprise both, CDR H3 and CDR L3 of Figure 21, it does not retain the specificity of antibodies comprising the all six CDRs mentioned in the claims. Hence, the objections under insufficiency of disclosure raised

above against the subject-matter of claims 1 of the main request and auxiliary request 1 likewise apply.

28. Accordingly, the requirements of Article 83 EPC are likewise not complied with.

Further remarks

Article 84 EPC

29. The board, in its communication dated 2 January 2020 (see point 14), also saw a lack of clarity regarding the relative functional terms "*strongly*" and "*minimally*" in feature c) of claim 1 of all claim requests on file (see section IV above), which had not been an issue before the examining division.

30. At the end of the oral proceedings, the board indicated that, if the binding affinity was indeed determined by the presence of at least three or five of the six CDRs shown in Figures 20 and 21, the feature "*binds strongly to LNCAP cells but not or only minimally to cells which lack expression of*" PSMA could be regarded as an inherent feature of the structurally defined antibodies.

31. The data submitted by the appellant (see document D37), do not support this argument. The humanised variant shown in Figure 1C differs from the murine antibody in three CDRs, but has a significantly lower binding affinity for PSMA positive cells than the murine antibody.

32. Document D37 does not help to overcome the clarity issue regarding the strong or minimal binding properties of the anti-PSMA monoclonal antibody/

fragment referred to in claim 1, since the presence of three or five murine CDRs in a humanised antibody/ fragment is not necessarily sufficient to retain the binding affinity of the parental murine antibody. It is uncontested that the substitution of a single amino acid in a CDR may reduce or even abolish the binding affinity of a humanised antibody (see above).

33. During the oral proceedings the appellant further submitted that the introduction into claim 1 of a concrete binding affinity of the claimed antibody/ fragment for defining the limits of strong or minimal binding was unnecessary since a pathologist as the skilled person used these functional criteria and knew what was meant.

34. However, the skilled person, as regards the subject-matter of claim 1, is not limited to a pathologist, but includes *inter alia* immunologists using antibodies for basic research purposes. Furthermore, a pathologist's assessment of an antibody's binding property is not an absolute criterion and differs between members of this profession. Claim 1 is also not limited to a pathologist as a reference for defining the limits of the claimed binding behaviour. Thus, the limits of a strong or minimal binding of the claimed antibody/ fragment, and hence, the functional limitation of the subject matter for which protection is sought also remained unclear
(Article 84 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated