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Datasheet for the decision of 7 July 2022

Case Number: T 2775/19 - 3.3.04

Application Number: 10711069.4

Publication Number: 2411408

IPC: C07K16/00, C07K16/10, C07K16/12, C07K16/28

Language of the proceedings: EN

Title of invention:
Soluble "heavy-chain only" antibodies

Patent Proprietors:
Erasmus University Medical Center Rotterdam
Craig, Roger Kingdon

Opponents:
Regeneron Pharmaceuticals, Inc.
Ablynx N.V.
Virnekäs, Bernhard

Headword:
Heavy-chain only antibodies/ERASMUS UNIVERSITY

Relevant legal provisions:
EPC Art. 56, 83, 84, 123(2), 123(3)

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
Claims - clarity (yes)
Amendments - extension beyond the content of the application as filed (no) - broadening of claim (no)
Inventive step - (yes)
Sufficiency of disclosure - (yes)

Decisions cited:
G 0003/14

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Case Number: T 2775/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 July 2022

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 August 2019 concerning maintenance of the European Patent No. 2411408 in amended form.**

Composition of the Board:

Chairman L. Bühler
Members: B. Rutz
D. Luis Alves

Summary of Facts and Submissions

I. The appeal by opponent 1 (appellant) lies from the decision of the opposition division that European patent No. 2 411 408 ("the patent") in amended form according to auxiliary request 5 meets the requirements of the EPC. The patent is entitled "*Soluble 'heavy-chain only' antibodies*".

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and on the grounds of Articles 100(b) and 100(c) EPC.

III. The opposition division decided that claims 1 and 2 of the main request (patent as granted) and of auxiliary requests 1 to 4 extended the subject-matter beyond the content of the application as filed (Article 123(2) EPC).

IV. Claim 1 as granted reads as follows:

"1. A method of producing a heavy chain-only antibody which binds specifically to an antigen comprising:
(a) immunising a non-human transgenic mammal with the antigen, wherein the mammal expresses heavy chain-only antibodies which lack a CH1 domain in the transcribed and processed heavy chain mRNA, and wherein the heavy chain-only antibodies are expressed from a transgenic locus in the mammal;
(b) isolating long-lived plasma cells or memory B-cells from the immunised mammal;
(c) isolating an mRNA population from cells derived from step (b);

(d) cloning a cDNA population derived from the mRNA isolated in step (c) into an expression vector and expressing the expression vector in a cell-line; and
(e) selecting at least one cell-line which produces a heavy chain-only antibody which binds specifically to the antigen,
wherein the mammal is a mouse or a rat."

V. With the statement of grounds of appeal the appellant submitted document D35.

VI. With the reply to the statement of grounds of appeal the patent proprietors ("respondents") promoted auxiliary request 5, which was allowed in opposition proceedings, to their main request and filed further auxiliary requests 1 to 23.

Claims 1 and 2 of the main request read as follows:

"1. A method of producing a heavy chain-only antibody which binds specifically to an antigen comprising:
(a) immunising a non-human transgenic mammal with the antigen, wherein the mammal expresses heavy chain-only antibodies, and wherein the heavy chain-only antibodies are expressed from a transgenic locus in the mammal, wherein the transgenic locus comprises one or more V gene segments, one or more D gene segments and one or more J gene segments, operationally linked to one or more heavy chain effector regions, wherein the V, D and J gene segments are naturally-occurring human V, D and J segments, and wherein each of the heavy chain effector regions lacks CH1;
(b) isolating long-lived plasma cells or memory B-cells from the immunised mammal;
(c) isolating an mRNA population from the cells isolated in step (b);

(d) cloning a cDNA population derived from the mRNA isolated in step (c) into an expression vector and expressing the cDNA in a mammalian cell-line; and
(e) selecting at least one mammalian cell-line which produces a heavy chain-only antibody which binds specifically to the antigen,
wherein the mammal is a mouse or a rat."

2. A method of producing a VH fusion protein which binds specifically to an antigen comprising:
(a) immunising a non-human transgenic mammal with the antigen, wherein the mammal expresses heavy chain-only antibodies, and wherein the heavy chain-only antibodies are expressed from a transgenic locus in the mammal, wherein the transgenic locus comprises one or more V gene segments, one or more D gene segments and one or more J gene segments, operationally linked to one or more heavy chain effector regions, wherein the V, D and J gene segments are naturally-occurring human V, D and J segments, and wherein each of the heavy chain effector regions lacks CH1;
(b) isolating long-lived plasma cells or memory B-cells from the immunised mammal;
(c) isolating an mRNA population from the cells isolated in step (b);
(d) cloning a cDNA population comprising cDNAs which encode a VH domain derived from the mRNA of step (c) into an expression vector such that a VH fusion protein, which may comprise a heavy chain effector region, is expressed in the mammalian cell-line; and
(e) selecting at least one mammalian cell-line which produces a VH fusion protein which binds specifically to the antigen,
wherein the mammal is a mouse or a rat."

VII. The board summoned the parties to oral proceedings and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VIII. With letters of 10 May 2022 and 25 May 2022 respectively, opponents 2 and 3, who are parties as of right, informed the board that they would not be attending the oral proceedings. With its letter of 19 May 2022 the appellant responded to the preliminary opinion of the board and, *inter alia*, provided arguments with regard to the auxiliary requests filed by the respondent.

IX. Oral proceedings before the board took place on 7 July 2022 (in the absence of opponents 2 and 3) in the form of a videoconference, as requested by the appellant and the respondents. At the end of the oral proceedings, the chairman announced the board's decision.

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

D2 X. Zou et al., "*Heavy chain-only antibodies are spontaneously produced in light-chain deficient mice*", J Exp Med 204(13), December 2007, 3271-3283.

D3 R. Janssens et al., "*Generation of heavy-chain only antibodies in mice*", PNAS 103(41), October 2006, 15130-15135

D4 WO 2006/008548

D7 M. K. Slifka et al., "*Humoral immunity due to long-lived plasma cells*", Immunity 8, March 1998, 363-372

D10 J. S. Babcook et al., "*A novel strategy for generating monoclonal antibodies from single, isolated lymphocytes producing antibodies of defined specificities*", PNAS 93, July 1996, 7843-7848.

D11 J. A. Coronella et al., "*Amplification of IgG VH and VL (Fab) from single human plasma cells and B cells*", Nucleic Acids Research 28(20), 2000, e85.

D16 H. R. Hoogenboom, "*Selecting and screening recombinant antibody libraries*", Nature Biotechnology 23(9), September 2005, 1105-1116.

D19 S. M. Anderson et al., "*New markers for murine memory B cells that define mutated and unmutated subsets*", Journal of Experimental Medicine 204(9), September 2007, 2103-2114.

D22a US 2007/0280945

D23 WO 2009/030237

D25 A. Lanzavecchia et al., "*Human monoclonal antibodies by immortalization of memory B cells*", Current Opinion in Biotechnology 18, 2007, 523-528.

D33 D. Drabek et al., "*Expression Cloning and Production of Human Heavy-Chain-Only Antibodies from Murine Transgenic Plasma Cells*", Frontiers in Immunology 7, December 2016, Article 619, 1-10.

D35 WO 2014/141192

XI. The appellant's arguments as far as relevant to the present decision are summarised as follows:

Main request

Claim interpretation and clarity (Article 84 EPC) "naturally-occurring V, D and J segments"

It was not clear whether the expression "naturally occurring" limited the V, D and J segments to unrearranged germ-line sequences or also included rearranged segments potentially including somatic mutations. Moreover, the fact that those segments "*must be capable of recombining*" as stated in the application

as filed (see page 29, lines 19 to 20) was not mentioned in the claims. Furthermore, even human germ-line sequences could not be distinguished from synthetic or artificial sequences or from natural sequences which had been mutated or engineered (see page 29, lines 12 to 14 of the application as filed), because not all naturally occurring human germ-line sequences had been sequenced yet and made available in publicly accessible databases.

"heavy chain effector region"

It was unclear from the wording of the claims whether the term "effector region" referred only to the constant region or whether it encompassed non-constant regions. It was also unclear whether this term, for example, encompassed a CH3-lacking constant region and/or a CH2-lacking constant region.

The term "effector region" described a feature of the heavy chain antibodies (HCAbs), i.e. at the protein level, whereas the other features of the transgenic locus were defined at the nucleic acid level. It was unclear how a transgenic locus could comprise such a proteinaceous "effector region".

"lacks CH1"

CH1 was a protein domain, whereas the reference to CH1 formed part of the definition of the transgenic locus in claims 1 and 2, i.e. at the nucleic acid level. This inconsistency of terminology cast doubt on the scope of the claims.

It was further unclear whether the term "lacks CH1" meant that the sequence lacked a whole CH1 domain or

part of a CH1 domain or whether "lacks CH1" indicated a lack of full or partial CH1 functionality, e.g. due to the introduction of a mutation.

"expressing the cDNA"

Based on the wording of claim 1 alone, the skilled person would be unsure whether "expressing the cDNA" required expression of the whole cDNA population.

"isolating long-lived plasma cells or memory B-cells from the immunised mammal"

The opposition division considered step (b) of claims 1 and 2 to encompass any enrichment in long-lived plasma cells (LLPCs) or memory B-cells (MBCs) from a crude cell preparation, but it was of the opinion that no particular level of enrichment was required. Adopting the opposition division's interpretation of step (b), however, did not allow third parties to determine whether they were operating inside or outside of the claimed methods, because the required level of enrichment was not defined in the claims, e.g. to distinguish from a tissue source in which the proportion of long-lived plasma cells or memory B-cells is enriched relative to a mammal as a whole.

"(c) isolating an mRNA population from the cells isolated in step (b);
(d) cloning a cDNA population derived from the mRNA isolated in step (c)"

Step (d) of claims 1 and 2 did not recite the "direct cloning" of a cDNA into a mammalian expression vector and did not disclaim the use of hybridoma or phage display methods to screen antibodies prior to cloning

of a cDNA into an expression vector. Instead, it only referred to the use of cDNA derived from (representing the coding sequence of) the (originally) isolated mRNA.

Applying the broadest technically meaningful interpretation, claims 1 and 2 instead encompassed the use of a variety of methods, such as transfection of cells, the generation of hybridomas and phage display methods.

Added subject-matter (Article 123(2) EPC)

The omission from claims 1 and 2 of the recombining capability of the V gene segment (see page 29, lines 19 to 22, of the application) resulted in an unallowable intermediate generalisation. Moreover, page 29, lines 19 to 21, of the description was not provided in the context of a method according to claims 1 and 2. In addition, page 29, lines 19 to 21, referred in parentheses to a heavy chain constant region, which "*may comprise several exons but excludes a CH1 exon*", whereas claim 1 did not refer to such a heavy chain constant region. Instead, claim 1 specified that "*each of the heavy chain effector regions lacks CH1*", which, if read in the context of a DNA sequence, could be interpreted as meaning that each heavy chain effector region lacked a CH1 exon as well as the associated non-coding regions. The fact that claims 1 and 2 did not reflect the precise language found at page 29, lines 19 to 21, indicated that the subject-matter of the claims was not directly and unambiguously derivable from the application as filed.

Page 31, lines 23 to 25, stated that "*For instance, the expression of all or part of a heterologous heavy chain*

Cγ locus devoid of CH1 will produce optionally some or all IgG isotypes, dependent on the IgG1, IgG2, IgG3 and IgG4 isotypes present in the heterologous IgG locus". This passage was not disclosed in the context of the claimed methods, but was provided in the context of a "*heavy chain constant region [that] essentially comprises at least one heavy chain constant region gene, which is expressed without a functional CH1 domain...*" (see first sentence of the preceding paragraph on page 31; the underlined words in this quoted passage are absent from claims 1 and 2). Moreover, page 31, line 23, was limited to the expression of all or part of a heterologous heavy chain Cγ locus, whereas claims 1 and 2 were silent regarding whether or not the "*transgenic locus*" was a "*Cγ locus*" (i.e. whether or not it was Cμ or Cδ-deficient). Thus, page 31, line 23, could not provide a basis for claims 1 and 2.

Page 47, line 1, similarly referred to "*Cγ constant regions*", which were not recited in claims 1 and 2. Moreover, the sentence at page 47, line 1, was found in Example 7 of the application as filed, which contained many features that were absent in claims 1 and 2. Thus, the application as filed did not directly and unambiguously disclose a method according to claims 1 and 2.

The large number of passages cited as a basis in the decision under appeal indicated that the application was treated as a 'reservoir' from which features pertaining to separate embodiments had been combined. This infringed Article 123(2) EPC.

Step (c) of claims 1 and 2 recited a step of: "isolating an mRNA population from the cells isolated

in step (b)", whereas the corresponding step in claim 34 as filed referred to: "isolating an mRNA population from cells derived from step (b)".

Page 24, lines 21 to 24, could not provide unambiguous support for this amendment because, firstly, it related to the isolation of mRNA from "*isolated plasma or memory cell populations*" rather than from long-lived plasma cells. Secondly, it was provided in the context of: "*B-cell isolation from bone marrow and lymph nodes, followed by B-cell purification using an antibody against a pan B-cell surface marker*" (see page 24, lines 4 to 6) rather than in the context of a method according to claims 1 and 2.

Extension of the scope of protection
(Article 123(3) EPC)

The deletion of the requirement for the mammal to express HCAbs "which lack a CH1 domain in the transcribed and processed heavy chain mRNA" resulted in the extension of the scope of protection. Applying the "broadest technically meaningful interpretation", a transgenic locus which comprised a mutated CH1 exon could lead to the production of mRNA containing a mutated CH1 domain, despite such an embodiment falling outside the scope of the granted claims.

Claims 1 and 2 as granted required expression of the whole of the expression vector, which would necessarily include non-cDNA components, such as cell-selectable marker cassette, signal sequences, Kozak sequences, (e.g. based on paragraph [0157] and Figure 18 of the patent), in addition to the cDNA. In contrast, claims 1 and 2 required expression only of the cDNA, but did not

require expression of any non-cDNA components of the expression vector.

Inventive step (Article 56 EPC)

The opposition division considered document D4 to represent the closest prior art and formulated the objective technical problem as the provision of an improved (less laborious) method of producing an HCAb which binds specifically to an antigen from a transgenic locus.

However, in view of the lack of a demonstrated technical effect across the scope of claim 1, the objective technical problem should be formulated in a less ambitious manner, namely as the selection of an alternative means of cloning antibody mRNA.

The claimed invention was obvious in view of document D4 in combination with common general knowledge. In particular, document D4 taught methods for the production of HCAbs using transgenic animals that comprised a transgenic locus and secreted these antibodies from plasma or B-cells (see, e.g., page 10, lines 3 to 6). It also taught that such antibodies could be recovered from B-cells of the spleen by standard cloning technology (see page 5, lines 22 to 23). "Direct cloning" methods would have been considered by the skilled person to be an example of standard cloning technology.

The skilled person working on HCAbs would also have considered prior art relating to any other types of antibodies (e.g. tetrameric) and would have had common general knowledge of molecular biology techniques in relation to isolation of antibody sequences. The

absence of CH1 in the heavy chain effector regions was of no technical relevance in view of the skilled person's goal of cloning antibody variable region sequences which were known to be the same in HCAbs and in tetrameric antibodies (see, e.g., documents D10, D11, D16, D22a, D23 and D25).

Document D2 would have been considered by the skilled person because it related to expression of HCAbs lacking a CH1 domain in rodents (see Abstract), i.e. the same technical field as the claimed invention. Instead of generating hybridomas, document D2 taught the direct cloning of antibody cDNA from the syndecan-positive (long-lived) plasma cells (see page 3278, right column, lines 3 to 5 and 10 to 14; and page 3279, sentence bridging right and left columns, and right column, lines 13 to 16) and provided a pointer and motivation to use direct cloning in the context of isolation of HCAbc DNA to simplify access to HCAbs. There was nothing inventive in further steps of cloning into an expression vector and expression in a cell line, as these steps were entirely standard in the field of recombinant technology. Thus, by combining the teaching of document D4 with that of document D2, in view of common general knowledge, the skilled person would have arrived at the claimed subject-matter.

An analysis of inventive step using the "partial problems" approach was justified because the cell population and cloning methods did not mutually influence each other to achieve technical success over and above the sum of each of their individual effects, and instead related to different, unrelated aspects of the method.

Since the selection of a population of cells that was enriched for long-lived plasma cells or memory B-cells was obvious based on document D4 combined with document D2 and the cloning methods were obvious from the combination of document D4 with any of documents D2, D10, D11, D16, D22a or D23, the claimed method was equally obvious.

Sufficiency of disclosure (Article 83 EPC)
Isolation of memory B-cells

The patent failed to disclose a method of isolating memory B-cells and/or any markers for doing so. Document D19 could not remedy this deficiency, because it was cited in a paragraph that related solely to the isolation of a "plasma cell population" and therefore the skilled person would have had no reason to consult this document when attempting to isolate memory B-cells. Moreover, document D19 lacked any concrete disclosure of a suitable method for isolating memory B-cells from immunised mice and rats. Therefore, even if the skilled person had consulted document D19, it would have been an undue burden to conduct the further scientific research required.

V segments

Document D35 in combination with document D33 taught that the majority of VH segments were unsuitable for generating HCAbs in a transgenic rodent. Moreover, according to the patent proprietors' later disclosure, the claimed methods only worked with a very small number of specific naturally occurring human V segments, and (only) in cases in which these were the only V segments provided in the transgenic locus (and also if the endogenous V segments were deleted or

inactivated). The skilled person would therefore have been unable to work the invention over the whole area claimed without undue burden.

Endogenous antibody loci

The patent referred to the use of transgenic mice as described in document D3, which disclosed that all of the heavy chain-only locus constructs cited therein were provided in a µMT background, thereby giving rise to a lack of (endogenous) surface IgM and a consequent block in B-cell development. Thus, serious doubts arose regarding whether the claimed methods would allow the production of HCAbs in a genetic background in which endogenous antibodies were present. In this situation, including in the context of there being no restriction on the types of human VH segments to be incorporated into the locus, no selective pressure for use of the transgenic locus according to the claims existed.

XII. The respondents' arguments as far as relevant to the present decision are summarised as follows:

Main request

Claim interpretation and clarity (Article 84 EPC)
"naturally occurring V, D and J segments"

The skilled person would understand that "naturally occurring V, D and J segments" referred to unrearranged germ-line sequences because after rearrangement those sequences were no longer referred to as segments. The skilled person carrying out the method and using the transgenic animal knew the source of the human sequences therein and whether or not they had been modified. It was clear from the context of the claim

that the V, D, J segments had to be capable of recombining because, otherwise, no HCAb would be generated in the transgenic mammal. Moreover, the skilled person could compare the sequences of the V, D, J segments with comprehensive databases of human germ-line variable region sequences, such as V BASE.

"heavy chain effector region"

The terms "constant region", "constant effector region" and "effector region" were used interchangeably in the patent. Step (a) of claims 1 and 2 stated that, in the transgenic HCAb locus, the heavy chain effector regions were "operationally linked" to the variable domain gene segments (VDJ segments). In addition, "each of the heavy chain effector regions" was required to "lack CH1". Thus, the skilled person understood that a "heavy chain effector region" referred to a heavy chain constant region, which normally included CH1. The skilled person also understood that one component of a transgenic locus was necessarily a nucleic acid.

"lacks CH1"

"Lacks CH1" was a feature of the transgenic locus and was therefore a nucleic acid feature. It meant that CH1 was not present in any of the effector regions of the locus.

"expressing the cDNA"

Since there was no other cDNA mentioned in the claims, the opposition division was correct in paragraph 9.4 of its decision that "*there is no doubt that the cDNA referred to corresponds to the cDNA population previously mentioned in the claims*".

"isolating long-lived plasma cells or memory B-cells from the immunised mammal"

Isolating long-lived plasma cells or memory B-cells from the immunised mammal required a deliberate selective enrichment, for example by FACS, to obtain the respective cell population. Merely using a crude cell preparation, e.g. from the spleen, was not "isolating". While this population did not have to be completely pure, it was useful for the subsequent steps, i.e. the efficient isolation of mRNA in sufficient quantities.

"(c) isolating an mRNA population from the cells isolated in step (b);
(d) cloning a cDNA population derived from the mRNA isolated in step (c)"

The opponent argued that the "comprising" language in claims 1 and 2 resulted in the claims encompassing methods that involved the generation of hybridomas from isolated LLPCs or MBCs, and then isolating mRNA from those hybridomas. However, step (c) referred to isolating an mRNA population from the cells isolated in step (b), i.e. the LLPCs or MBCs that were isolated from the immunised mammal. If one were to perform an intermediate step of generating hybridomas, then the

mRNA would not subsequently be isolated "from the cells isolated in step (b)", as required by claims 1 and 2.

Added subject-matter (Article 123(2) EPC)

A basis for the core of claim 1 could be found, e.g., in claim 34 as filed, with a corresponding passage being provided on page 22 (lines 10 to 21) of the application as filed. A few features of this central teaching had been narrowed down or clarified to arrive at claim 1.

Mice and rats were "*especially preferred*" transgenic mammals for use in the methods of the invention (see, e.g., page 32, lines 21 to 23, of the application).

It was implicit from the teaching on page 22, lines 12 to 14, itself that the "heavy chain-only antibodies that lack CH1 functionality" were expressed from a transgenic locus. This was because these HCAbs were expressed by "a non-human transgenic mammal". Thus, the skilled person understood that the "transgenic" nature of the mammal related to the locus encoding the HCAbs that were expressed. Indeed, there was no other reason for specifying that the mammal was "transgenic".

Accordingly, claim 1 merely rendered explicit what was already implicit in the teaching on page 22.

Furthermore, the application stated explicitly on page 23, lines 1 to 3, that the method involved expression of HCAbs from a transgenic locus: "*The method is suited for the isolation of heavy chain-only antibodies, whether produced naturally in the host organism, such as llama, or as a result of an expressed transgenic locus in a non-human host organism*". It was the

production of HCAbs "*as a result of an expressed transgenic locus in a non-human host organism*" that corresponded to the non-human transgenic mammal in step (a) on page 22, lines 12 to 14.

Claim 1 specified that the transgenic locus comprised V, D and J gene segments operationally linked to heavy chain effector regions. A basis for this could be found, e.g., in the definition provided for "*a 'heavy chain-only locus' in the context of the present invention*" in the section entitled "*The Heterologous Heavy chain-only Locus*" (see page 28, lines 24 to 27, of the application).

A basis for the naturally occurring human V, D and J segments could equally be found in the section entitled "*The Heterologous Heavy chain-only Locus*". Page 29, line 12, taught that: "*The term 'V gene segment' encompasses a naturally occurring V gene segment derived from a vertebrate, including camelids and human*". Page 29, line 32, disclosed that: "*VH coding sequences*" (i.e. V, D and J segments) "*may be derived from a naturally occurring source*". Page 30, line 12, taught that: "*In the context of the present invention, the terms 'a D gene segment' and 'a J gene segment' include naturally-occurring sequences of D and J gene segments. Preferably, the D and J gene segments are derived from the same vertebrate from which the V gene segment is derived*". Page 30, line 24, reiterated: "*D and J gene segments may be derived from naturally-occurring sources*". Finally, page 30, line 31, read: "*The V, D and J gene segments are preferably derived from a single vertebrate species. This may be any vertebrate species but is preferably a human*". Therefore, there was an explicit preference for using human V, D and J gene segments in the transgenic loci

of the invention, and naturally occurring human V, D and J segments were clearly envisaged.

The limitation in claim 1 that the HCAb were expressed from a locus in which "*each of the heavy chain effector regions lacks CH1*" had a basis, e.g., on page 29, line 19, which stated that: "*The V gene segment must be capable of recombining with a D gene segment, a J gene segment and a heavy chain constant (effector) region (which may comprise several exons but excludes a CH1 exon) …*". Furthermore, at page 31, line 23, the application described an exemplary transgenic locus of the invention, "*a heterologous heavy chain Cγ locus devoid of CH1*". Moreover, at page 47, line 1, the technical reason for ensuring that the effector regions lack CH1 was given: "*The CH1 regions have been deleted from the human Cγ to allow the production of human heavy chain-only antibodies …*". Consistent with these teachings, the exemplary V4 and V18 loci in Figure 1 of the application were shown to lack CH1 in each of the constant regions. Therefore, the application disclosed that one way of producing "*heavy chain-only antibodies that lack CH1 functionality in the transcribed and processed heavy chain mRNA*" (in step (a) on page 22) was to use heavy chain effector regions that lack CH1.

Page 22, line 17, referred to mRNA isolation from "cells derived from step (b)", with LLPCs or MBCs being isolated in step (b). The application explained at page 24, line 21, that "*Following mRNA isolation from isolated plasma or memory cell populations, cDNA … is cloned into the expression vector of choice …*". Therefore, there was an explicit teaching to isolate mRNA directly from the plasma and memory cells isolated in step (b) of the method. Consistent with this, the

application taught that these cells were "*a source of HCAb mRNA*" at page 26, line 19.

Step (d1) on page 22 referred to expressing the cDNA in "*a cell-line of choice*". At line 29 on the same page, the application taught that "[t]*he cell-line of choice is preferably of mammalian origin*".

In summary, there was a basis in the application as filed for all of the narrowing-down and clarifying amendments that had been made to the core teaching at page 22, lines 10 to 21. Many of these amendments involved limitations to preferred features. Furthermore, the skilled person would have been guided towards this combination of features by Example 7. In particular, a mouse expressing HCAb from a transgenic locus that contained naturally occurring human V, D and J gene segments operationally linked to heavy chain effector regions that lacked CH1 was immunised, with subsequent isolation of mRNA directly from LLPCs and expression of cDNA in a mammalian cell line.

Extension of the scope of protection (Article 123(3) EPC)

A transgenic mammal that expressed HCAbs from a locus in which each of the effector regions lacked CH1 (as specified in step (a) of claims 1 and 2) necessarily had to express HCAbs "which lack a CH1 domain in the transcribed and processed heavy chain mRNA" (as specified in step (a) of granted claims 1 and 2).

Therefore, omission of the feature "*which lack a CH1 domain in the transcribed and processed heavy chain mRNA*" from step (a) of claims 1 and 2 of the main

request did not broaden the scope of the granted claims.

Both "expressing the expression vector" into which the cDNA had been cloned (as specified in granted claim 1) and "expressing the cDNA" that was present in the expression vector (as specified in claim 1 of the main request) required the expression of the cDNA and permitted the expression of any additional genes in the expression vector.

In the context of granted claim 1, the skilled person understood the expression step to require nothing more than expressing the HCAb-encoding cDNA within the vector – that was the purpose of step (d), as confirmed by step (e), in which antigen-specific HCAb-expressing cell-lines were selected. Indeed, the HCAb cDNA was the only component of the expression vector that was specified in granted claim 1(d).

Inventive step (Article 56 EPC)

Document D4 was the closest prior art and related to methods for obtaining HCAbs and VH domains by immunising mice or rats that contained a transgenic heavy chain-only locus.

Claim 1 could be distinguished from this method for at least three reasons. Firstly, step (b) of claim 1 required the isolation of LLPCs or MBCs, whereas D4 taught the isolation of "*a cell or tissue expressing an antigen-specific, heavy chain only antibody of interest*" (see page 9, lines 13 to 14). Secondly, step (c) of claim 1 required the isolation of mRNA from the cells isolated in step (b) (i.e. the isolated LLPCs or MBCs). In contrast, D4 taught that "*a hybridoma from*

the cell or tissue of step (b)" had to be produced and, subsequently, HCAb mRNA was cloned from the hybridoma (see page 9, lines 15 and 16). Thirdly, step (e) of claim 1 required the screening of mammalian cell lines to select those producing antigen-specific HCAbs. In contrast, D4 merely envisaged "*subsequent production*" of HCAbs (using mRNA cloned from hybridomas) in a heterologous expression system (see page 9, lines 16 to 18). The heterologous expression system was not used as a means for screening the HCAbs. Consistent with this, the hybridomas were subjected to analysis in Example 1 of document D4 (see page 46, lines 14 to 21) before the "subsequent production" in a heterologous expression system took place.

Unlike the methods of document D4, the claimed methods enabled the identification of antigen-specific HCAb and VH fusion proteins without the use of phage display or hybridoma generation. This resulted in the claimed methods being less laborious as well as simpler for efficiently producing antigen-specific HCAb or VH fusion proteins than those described in document D4.

The inventors were the first to realise that the generation of hybridomas and phage display could be bypassed by directly cloning HCAb-encoding mRNA from isolated LLPCs or MBCs into mammalian expression vectors and screening the transfected mammalian cells. They had previously expected the number of soluble antigen-specific HCAb-producing cells to be too low, due to the rare nature thereof, in a mouse or rat carrying a transgenic locus comprising naturally occurring human VDJ segments to allow the laborious phage display and hybridoma techniques to be avoided. That is why such techniques were presented and used in document D4. There was nothing in the prior art that

would have prompted the skilled person to simplify the inventors' original methods to arrive at the methods claimed.

Sufficiency of disclosure (Article 83 EPC)
Isolation of memory B-cells

Document D7 was an article cited in paragraph [0011] of the patent. This document provided an exemplary way of isolating memory B-cells from mice. D19 was an article that was cited in paragraph [0055] of the patent. This document provided markers that could be used to identify mouse memory B-cells, including CD73, CD80 and CD95. Document D19 taught that: "*Up-regulation on memory cells of the most important surface proteins – CD73, CD80, and CD95 – was found … This confirms the generality of these markers …*"(see page 2109, right-hand column, last two sentences).

V segments

Document D35 noted that some subclasses of human VH gene segments generated high-affinity HCAb more efficiently than others. However, it did not show that there were human VH segment repertoires that were incapable of generating HCAb in a transgenic mouse or rat. In any event, the invention was not a new form of a transgenic locus that produced heavy chain-only antibody, but was a method that was generally applicable to transgenic mice and rats that expressed HCAbs.

Endogenous antibody loci

The burden was on the opponents to provide evidence for their allegation that "*there are serious doubts*

regarding whether the claimed methods would enable the production of HCAb in a genetic background in which endogenous antibodies are present". This allegation was incorrect and was not substantiated by any evidence.

XIII. The appellant requested that the decision of the opposition division be set aside and that the patent be revoked.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

Main Request

Claim interpretation and clarity (Article 84 EPC)
"naturally occurring human V, D and J segments"

1. The board recognises that in the field of transgenic technology it can be difficult or even impossible to distinguish naturally occurring biological sequences from modified or artificial sequences if the origin of the sequence is not known. In the present case, however, the transgenic mouse or rat comprises a transgenic locus with V, D and J segments naturally occurring in humans, i.e. the origin of the sequences is defined. The segments are not endogenous to the mouse or rat because they are in a "transgenic locus" and are "human". As they are "naturally-occurring human V, D and J segments" they have been introduced without modifying their sequences. For a given transgenic animal this can be verified by the skilled person by comparing the transgenic locus with known human sequences, e.g. in commonly known databases. The fact that not all potentially existing human germ-line

sequences of V, D and J segments might be present in the respective databases is not an impediment in this respect, as unknown human sequences cannot be used in the construction of transgenic animals either.

2. It is implicit from the purpose and outcome of the claimed method, i.e. the production of an HCAb, that the V, D and J segments have to be capable of recombining with each other in the transgenic mammal. The way in which the transgenic mammal was generated thus defines the origin and the identity of the V, D, J segments. The expression "naturally occurring human V, D, J segments" is clear.

"heavy chain effector region"

3. Claims 1 and 2 require that the "heavy chain effector region" is to be "operationally linked" to the other segments in the transgenic locus. The term thus refers to a part of the transgenic locus, i.e. a genomic nucleic acid sequence encoding the heavy chain effector region of the expressed antibodies.

4. The terms "*constant region*", "*constant effector region*" and "*effector region*" are used interchangeably in the patent and are considered by the skilled person to mean the same. This excludes the interpretation put forward by the appellant that non-constant regions could be included in those regions. The fact that only CH1 is mentioned in the claim and that other parts of the heavy chain effector region, such as CH2 and CH3, are not further defined does not render the claim unclear.

"lacks CH1"

5. The wording "lacks" excludes speculation whether only a part of CH1 could be lacking or whether CH1 could be mutated or not functional in the expressed antibody. The board in this respect agrees with the respondents that effector regions that lack CH1, that exclude a CH1 exon or that have had CH1 domains deleted all correspond to the same technical teaching. The fact that non-coding flanking regions of the CH1 exon are not mentioned in the claim does not affect the clarity of the claim. The claim wording merely leaves it open whether upon deletion of the CH1 exon also the non-coding flanking regions (introns) are modified or deleted.

"expressing the cDNA"

6. The appellant argued that it was unclear whether the whole cDNA population generated in step (d) was expressed or only a single cDNA.

7. The board agrees with the decision under appeal that "*there is no doubt that the cDNA referred to corresponds to the cDNA population previously mentioned in the claims*". This understanding prevails on an objective reading of the claim through the eyes of the skilled person. In the context of the claimed method the skilled person knows that when generating antibodies against a target only a few clones will have the required binding to the antigen. The selection in step (e) is therefore necessary and requires the expression of the whole or at least a major part of the cDNA population to select from and not only a single cDNA.

"isolating long-lived plasma cells or memory B-cells from the immunised mammal"

8. This expression was present in the claims as granted and is thus not open to an objection of lack of clarity (see decision G 3/14, OJ 2015, A102).

9. The appellant considers that a crude cell preparation from an organ in which those cells were present (e.g. the spleen) was sufficient for "isolating" the cells. The respondents argue that a crude cell preparation could not be considered "isolating" but that at least a partial enrichment of the cells by other means was required by the claim.

10. The skilled person interprets the term "isolating" as meaning to separate the cells as far as possible from other cells. This can be achieved by the methods taught in the patent, e.g. flow-cytometry with specific markers (see e.g. paragraph [0054] of the patent and Example 7) but does not prescribe a specific degree of purity of the cells.

"(c) isolating an mRNA population from the cells isolated in step (b);
(d) cloning a cDNA population derived from the mRNA isolated in step (c)"

11. Step (c) refers to the isolation of mRNA from the cells isolated in step (b), which excludes the "*generation of hybridomas from the isolated long-lived plasma cells or memory B-cells, and then isolating mRNA from both the hybridomas and the long-lived plasma cells or memory B cells*" as suggested by the appellant.

12. With regard to step (d) the skilled person reads this step such that "a cDNA population derived from the mRNA" refers to a direct copy of the mRNA (e.g. by reverse transcription) and excludes *"hybridoma or phage display methods to screen antibodies prior to cloning of a cDNA into an expression vector*" as argued by the appellant.

13. In conclusion, the claims are clear.

Added subject-matter (Article 123(2) EPC)
"each of the heavy chain effector regions lacks CH1"

14. The feature "lacks CH1" is synonymous with "excludes a CH1 exon" (see point 5. above) and thus finds a basis on page 29, lines 19 to 21, of the application as filed. The skilled person understands from the context of the claims and the application as a whole that a heavy chain effector region which lacks CH1 is generated by excluding the CH1 exon from the transgenic locus or from the processed mRNA. Other passages of the application as filed, referred to by the respondents, (e.g. page 31, line 23: "*the expression of all or a part of a heterologous heavy chain Cγ locus devoid of CH1*" and page 47, line 1 "[t]*he CH1 regions have been deleted from the human Cγ constant regions to allow the production of human heavy chain-only antibodies as described (Janssens et al (2006) PNAS, 103, 15130-15135)*") also reflect this general teaching. The fact that the latter two passages refer to Cγ while the claim is not limited in that respect would not prevent the skilled person from considering the disclosure to be applicable also to other constant regions (see, e.g., Figure 1, which depicts also Cμ lacking the CH1 domain).

15. The appellant argued that the passage on page 29 of the application as filed contained the requirement that "the V gene segment must be capable of recombining with a D gene segment, a J segment an a heavy chain constant (effector) region". Leaving out this requirement in claims 1 and 2 resulted in added subject-matter.

16. The skilled person reading claims 1 and 2 with common general knowledge, however, understands that for obtaining heavy chain only antibodies (HCAb) in a transgenic mouse or rat the V, D and J segments and the heavy chain constant (effector) region have to be capable of recombining with each other to generate a functional heavy chain. This feature is therefore implicit and its omission does not change the subject-matter.

"naturally-occurring human V, D and J segments"

17. The appellant argued that page 28, lines 24 to 27, of the application represented "*boiler plate passages that are not provided in the context of the claimed methods*". The board does not agree, because the passage cited is in a section entitled "*The Heterologous Heavy chain-only Locus*", which discloses the different properties of this locus and thus relates to the claimed method.

18. In view of the interpretation of the claims provided in points 1. and 2. above, the use of "naturally-occurring human V, D and J segments" finds basis in the application as filed, for example on page 29, lines 12 to 22, and page 30, lines 12 and 13.

"isolating an mRNA population from the cells isolated in step (b)"

19. The appellant considered that amending "from the cells derived from step (b)" to "from the cells isolated in step (b)" added subject-matter because Example 7 was restricted to specific conditions and page 24, line 21, did not apply to "long-lived plasma cells", but only to "isolated plasma or memory cell populations".

20. The person skilled in the art, however, reads the passage on page 24 in the context of the method disclosed on page 22, lines 10 to 28, which refers to "*long-lived plasma cells or memory B-cells*" and having regard to the further reference to "*B-cell populations enriched in long-lived plasma cells or memory cells*" on page 23, line 12. The instruction on page 24: "*Following mRNA isolation from isolated plasma or memory cell populations*" thus also discloses mRNA isolation from the sub-set of long-lived plasma cells (LLPCs).

Combination of different parts of the disclosure

21. Two main passages relate to the claimed method in the application as filed: the section on pages 22 to 24 discloses the method steps and, secondly, the section on pages 28 to 32 discloses the transgenic animal.

22. Starting from claim 34 as filed, the claimed method is further limited by (i) restricting "lack CH1 functionality in the transcribed and processed heavy chain mRNA" to "wherein each of the heavy chain effector regions lacks CH1" (see page 29, line 21: "*excludes a CH1 exon*"); (ii) restricting the cell line to a mammalian cell line (see page 22, line 29);

restricting "from the cells derived from step (b)" to "from the cells isolated in step (b)" (see page 24, line 21, and Example 7 as a pointer); (iv) defining the transgenic locus in the transgenic mammal (see page 23, lines 2 to 3, page 28, line 24 to 27; page 31, lines 8 to 11, line 31, line 29 to page 32 line 2) and (v) restricting the transgenic mammal to mouse or rat (see page 32, lines 21 to 23).

23. The combination of these limitations is directly and unambiguously derivable from the application as filed as a preferred embodiment of the method to generate HCAbs or VH fusion proteins. In particular, the skilled person would have recognised that deleting CH1 ("lacks CH1") instead of only disabling its functionality was preferred as was the use of a mammalian cell line and mouse or rat as transgenic mammals. The clarification of "cells derived from" to "cells isolated from" corresponds to the teaching of the application as a whole that direct cloning of mRNA from the selected cell types is feasible and yields functional HCAbs. The combination of preferred embodiments is also supported by the specific methods disclosed in the Examples (see e.g. Example 7).

24. In conclusion, the claims satisfy the requirements of Article 123(2) EPC.

Extension of the scope of protection (Article 123(3) EPC)

"wherein each of the heavy chain effector regions lacks CH1"

25. The appellant considers that the omission of the reference to "the transcribed and processed heavy chain mRNA" (see section IV. above) in the amended claims extended the scope of protection.

26. The claims as granted included the feature "*the mammal expresses heavy-chain only antibodies which lack a CH1 domain in the transcribed and processed heavy chain mRNA*". In the claims in hand the feature reads "*the mammal expresses heavy chain-only antibodies, and wherein the heavy chain-only antibodies are expressed from a transgenic locus in the mammal, wherein the transgenic locus comprises one or more V gene segments, one or more D gene segments and one or more J gene segments, operationally linked to one or more heavy chain effector regions, wherein the V, D and J gene segments are naturally-occurring human V, D and J segments, and wherein each of the heavy chain effector regions lacks CH 1*". The production of an HCAb in a transgenic animal, however, necessarily passes through the step of transcription and processing of the heavy chain mRNA. The situation in which each of the heavy chain effector regions in the transgenic locus lacks CH1 (i.e. in the genome) is therefore encompassed by the lack of a CH1 domain in the transcribed and processed heavy chain mRNA.

"expressing the cDNA"

27. The appellant further argued that "expressing the vector" was more limited than "expressing the cDNA" because the former involved the expression of all elements of the vector including some non-coding sequences and markers.

28. In the context of the claimed method the expression of a cDNA necessarily has to involve the expression of a vector, be it a plasmid, a virus or any other means which brings the cDNA into the cell and allows for its expression. The skilled person, moreover, knows that in

the context of the claimed method cloning a cDNA into an expression vector only makes sense if said expression vector is also used for expressing the cDNA.

29. In conclusion, the claims do not extend the scope of protection within the meaning of Article 123(3) EPC.

Inventive step (Article 56 EPC)

30. Both parties agree that document D4 can be considered as the closest prior art. In view of the interpretation of claim 1 above, a first difference relates to the cell population used for isolating the mRNA ("long-lived plasma cells or memory B-cells from the immunised mammal") and a second difference relates to the direct cloning of the cDNA derived from the isolated mRNA into the vector used for expressing the cDNA in a mammalian cell-line.

31. While the appellant considers that the patent did not show that these differences had any effect, the respondents are of the opinion that they resulted in a less laborious and simpler method for efficiently producing antigen-specific HCAb or VH fusion proteins.

32. In view of the finding provided below that the claimed method is not obvious over the cited state of the art, even if the objective technical problem put forward by the appellant ("*alternative method*") is adopted, it is not necessary to determine whether the effect proposed by the respondents is indeed obtained by the claimed method. In the following paragraphs, the claimed method is analysed in view of the less ambitious problem proposed by the appellant.

33. Document D4, while generally stating that "*heavy-chain only antibodies ... are secreted by plasma or B cells*" (see page 10, lines 3 to 6), requires either the production of a hybridoma from the antibody-expressing cells or tissue or the cloning and phage display of a VH locus from mRNA derived from the antigen-expressing cells or tissue (see, e.g., claims 39 and 40). Isolation of LLPCs or memory B-cells (MBCs) and direct cloning of cDNA from those cells as well as expression and selection in mammalian cells is not disclosed in document D4. Those features are, moreover, not merely aggregated, but work in combination to produce HCAbs or VH fusion proteins. It is the isolation of the specific cell types that enables the direct cloning of the cDNA of HCAbs. The appellant's attempt to address those features as "partial problems" is therefore not considered persuasive.

34. The skilled person looking for an alternative method for producing HCAbs finds no indication or motivation in document D4 to omit the steps of hybridoma generation or phage display, which are disclosed as essential in document D4 (see, e.g., page 9, lines 10 to 29). Also, the passage on page 10, lines 15 to 17, in document D4, which states that "*high levels of heavy-chain only antibody present in isolated plasma (provided that the CH1 domain has been eliminated from all antibody classes present in the recombinant locus)*" does not refer to specific cell types but only to "*isolated plasma*" and does not indicate whether the levels were high enough to allow omission of hybridoma generation of phage display. Page 19, lines 3 to 7, of document D4 states that "*nucleic acid sequences may be isolated from transgenic mammals according to the present invention and used to produce VH domain heavy chain-only chain antibodies or bi-specific/bifunctional*

complexes thereof, using recombinant DNA techniques which are familiar to those skilled in the art", but equally does not provide the skilled person with an indication that those nucleic acid sequences can be directly introduced into mammalian cells for expression without a prior selection step. The remaining documents cited by the appellant also would not have motivated the skilled person to modify the method disclosed in document D4, because they relate to tetrameric (standard) antibodies (documents D10, D11, D16, D22a, D23, D25).

35. The appellant argued that the skilled person nevertheless would have transferred the teaching in those documents to the method disclosed in document D4.

36. The board disagrees because the skilled person did not know whether the number of soluble antigen-specific HCAb-producing cells and the amount of mRNA therein would be sufficient in a mouse or rat carrying a transgenic locus comprising naturally occurring human VDJ segments to allow direct cloning. In view of the available teaching for HCAbs (see document D4) which required hybridoma generation or phage display the skilled person could not expect this and would therefore not have transferred the teaching of documents which concerned direct cloning of tetrameric antibodies to a method for producing HCAbs.

37. Moreover, none of those documents discloses or suggests the direct cloning of cDNA from LLPCs or MBCs into a mammalian expression vector for selection in mammalian cells.

38. Document D2 relates to a specific mouse strain ("light-chain deficient") in which HCAbs are spontaneously

produced (see title and abstract). The document does not teach direct cloning of antibody encoding sequences from LLPCs or MBCs for expression in mammalian cells, but describes analysis of the sequences by RT-PCR from syndecan (CD138) positive cells (see page 3277, right-hand column, first full paragraph). In view of the problems with generating hybridomas from L-chain deficient mice, the authors suggest increasing the cell population of H chain-only Ig producing progenitors (see paragraph bridging pages 3280 and 3281), i.e. they do not suggest direct cloning, but propose to ameliorate the known hybridoma technique.

39. As document D2 is limited to a specific mouse strain, it does not disclose whether direct cloning was possible from a mouse or rat carrying a transgenic locus comprising naturally-occurring human VDJ segments. Moreover, the analysis of sequences by RT-PCR cannot be equated to and provide a sufficient indication for success of direct cloning of the respective sequences. Furthermore, also document D2 does not disclose the direct cloning of cDNA from LLPCs or MBCs into a mammalian expression vector for selection in mammalian cells.

40. The skilled person, even if considering document D2 when aiming to find an alternative method for the generation of HCAbs, would not have arrived at the claimed invention.

41. The method claimed in claims 1 and 2 is inventive.

Sufficiency of disclosure (Article 83 EPC)
Isolation of memory B cells

42. Documents D7 (cited at paragraph [0011] of the patent) and D19 (cited at paragraph [0055] of the patent) provide exemplary ways to identify and isolate mouse memory B cells. The appellant argued that the skilled person would not have consulted document D19 because it was cited in a passage relating exclusively to plasma cells. This is not convincing because the citation is introduced with the sentence "*Other cell surface markers can also be used to isolate these cells (e.g. Anderson et al. …)*" and the preceding paragraph [00054] mentions both plasma cells and memory B cells. The skilled person would therefore have expected to find relevant teaching in the cited document for both cell types. The appellant has not provided evidence that the teaching of those documents was insufficient to enable the skilled person to obtain those cells from mice or rats.

V segments

43. The teaching of document D35 that some subclasses of human VH gene segments generate high affinity HCAb more efficiently than others does not represent sufficient evidence that a majority of VH gene segments are not suitable for the method as claimed. In particular, the claimed method does not require a certain efficiency for the generation of HCAbs or a certain affinity of the resulting HCAbs.

Endogenous antibody loci

44. The appellant did not provide evidence that "*a genetic background in which endogenous antibodies are present*"

would not allow the claimed method to be carried out. The use of certain mice strains in the Examples 1, 2 and 7 of the patent (see document D3, cited therein, for the µMT genetic background of the mice) does not show that the invention could not be carried out in other genetic backgrounds.

45. In conclusion, the appellant has not raised serious doubts substantiated by verifiable facts that the claimed method could be carried out by a person skilled in the art. In particular, the appellant has not shown that the isolation of MBCs would put an undue burden on the skilled person. Equally, the presence of endogenous VH regions in mice or rats has not been shown to impede the claimed method. Finally, the reference to specific VH segments which are shown to result in more efficient antibody production in post-published document D35 does not provide evidence that there are human VH segment repertoires that are incapable of generating HCAbs in a transgenic mouse or rat.

46. The patent discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

I. Aperribay L. Bühler

Decision electronically authenticated