Datasheet for the decision
of 29 May 2008

Case Number: T 1154/07 - 3.3.08
Application Number: 99917814.8
Publication Number: 1051493
IPC: C12N 15/13
Language of the proceedings: EN
Title of invention: Method for producing antibody fragments
Applicants: UNILEVER PLC, et al
Headword: Antibody fragments/UNILEVER
Relevant legal provisions: EPC Art. 56
Relevant legal provisions (EPC 1973): -
Keyword: "Inventive step (no)"
Decisions cited: -
Catchword: -
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DECISION of the Technical Board of Appeal 3.3.08 of 29 May 2008

Appellants: UNILEVER PLC et al
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Representative: Newbould, Frazer Anthony
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Composition of the Board:
Chairman:     L. Galligani
Members:      T. J. H. Mennessier
              C. Heath
Summary of Facts and Submissions

I. The applicants (appellants) lodged an appeal against the decision of the examining division of 9 January 2007 refusing the European patent application No. 99 917 814.8 with publication number 1 051 493. The application entitled "Methods for Producing Antibody Fragments" originated from an international patent application published as WO 99/37681.

II. The decision was based on the request filed at the oral proceedings held on 30 November 2006 (claims 1 to 9) which was refused for reasons of lack of inventive step (Article 56 EPC), in view of document D4 (see Section VIII, infra) taken as the closest prior art in combination with document D5 (see Section VIII, infra).

III. On 18 May 2007, the appellants filed a statement setting out the grounds of appeal which was accompanied by a main request, corresponding exactly to the request on which the decision was based, and an auxiliary request.

IV. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

V. On 11 March 2008, a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was sent to the appellants.

VI. On 27 May 2008, in reply to the Board's communication the appellants filed a letter which was accompanied by
a main request (claims 1 to 4) to replace the main and auxiliary requests of 18 May 2007.

Claims 1 to 4 read:

"1. A naïve expression library comprising a repertoire of nucleic acid sequences cloned from a non-immunised source, each nucleic acid sequence encoding a variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains and derived from a camelid."

"2. A library according to claim 1 wherein the repertoire of nucleic acid sequences is derived from lymphoid cells."

"3. A library according to claim 1 or 2 wherein the repertoire of nucleic acid sequences is derived from cDNA clones."

"4. A method of preparing a naïve library according to claim 3 comprising providing a repertoire of mRNA from a non-immunised source, treating the obtained RNA with a reverse transcriptase to obtain the corresponding cDNA and cloning the cDNA, with or without prior PCR amplification, into an expression vector."

VII. Oral proceedings took place 29 May 2008.

VIII. The following documents are referred to in the present decision:

The submissions made by the appellants, insofar as they are relevant for the decision, may be summarised as follows:

Inventive step (Article 56 EPC)

Document D5 represented the closest prior art. Having regard to its disclosure, the technical problem to be solved was the provision of a library of high affinity antibodies from a small repertoire.

Document D5 stated that to isolate high affinity libraries from "naïve" libraries, size was the key factor, small scale libraries allowing only the isolation of low affinity antibodies. Therefore, the skilled person would have been discouraged to start from a library of small size such as a "naïve" library of nucleic acid sequences encoding a variable domain of a heavy chain derived from an immunoglobulin devoid of light chains and derived from a camelid. Document D5 showed that improving promiscuity between light and heavy chains was a requisite for improving the selection of high affinity antibodies. As the aforementioned camelid immunoglobulins were deprived of light chains, choosing as a source of mRNA cells from a non-immunised camelid would have been a counter-productive choice.

If document D4 were to be regarded as the closest state of the art, the invention was also inventive, as the use of non-immunised camelids as a source of nucleic
acid sequences was described therein only with respect to the preparation of antibodies by the hydridoma technology (as expressed in the sentence found on page 9, line 42 which reads "The preparation of antibodies can also be performed without a previous immunization of Camelids"). The combined use of phage display and of a non-immunised source separately described in the same document to carry out the method according to claim 4 represented an inventive selection of technical features.

X. The appellants requested that the decision of the examining division be set aside and that a patent be granted on the basis of the main request of 27 May 2008.

Reasons for the Decision

Inventive step (Article 56 EPC)

1. The inventive step assessment is particularly focused on the subject-matter of claim 4 which is a method for preparing a naïve library according to claim 3, this library being a particular embodiment of a library according to claim 1 or 2. The said library consists of a collection of nucleic acid sequences, each encoding a variable domain of a heavy chain derived from an immunoglobulin devoid of light chains, which have been cloned from a source, such as lymphocytes, derived from a non-immunised camelid. Such a library is useful for the preparation of antibodies or fragments thereof (see Examples 1 to 5, on pages 13 to 20 in the application). The method of claim 4 involves a series of steps, namely, in sequence, the provision of a repertoire of
mRNA from the non-immunised source, the treatment of the same with a reverse transcriptase to obtain cDNA and the cloning of that cDNA into an expression vector. These steps may be performed as illustrated in the description using the phage display technique.

2. Document D4 (rather than document D5, as argued by the appellants) is regarded by the board as the closest state of the art. Indeed, document D4 describes the preparation of libraries comprising a repertoire of nucleic acid sequences, each encoding a variable domain of a heavy chain derived from an immunoglobulin naturally devoid of light chains such as a camelid immunoglobulin, whereas document D5 focuses on human antibody libraries prepared by phage display aiming thereby at evaluating whether for the preparation of those libraries phage display could replace hybridoma technology.

3. The preparation of libraries comprising a repertoire of nucleic acid sequences, each encoding a variable domain of a heavy chain derived from an immunoglobulin devoid of light chains, are generally described on pages 8 (starting from line 5) and 9 (from line 1 to line 34) of document D4. It comprises the steps of providing a repertoire of mRNA from antibody producing lymphoid cells (see page 8, lines 19 to 20 and 58) taken from a camelid (see page 8, line 7 to 14), reacting the obtained RNA with a reverse transcriptase in order to obtain the corresponding cDNA (see page 9, line 1) and cloning the cDNA, with or without prior PCR amplification, into an expression vector (see page 8, lines 19 to 20 and page 9, lines 2 to 24). The use of cells from a camelid previously immunised as a source
of nucleic acid sequences is referred to twice on page 9 (see lines 25 to 27 and lines 48 to 50).

4. In view of document D4, the technical problem to be solved may be regarded as the provision of an alternative method of preparing a library comprising a repertoire of nucleic acid sequences, each encoding a variable domain of a heavy chain derived from a cameld immunoglobulin naturally devoid of light chains, in view of the preparation of antibodies, the solution thereto being a method according to claim 4, i.e. a method using as a source of mRNA cells from a non-immunised camelid, the latter requirement representing the only difference between the claimed method and the disclosure of document D4.

5. The question to be answered is whether at the relevant filing date it would have been obvious to the skilled person to replace the pre-immunised source by a non-immunised source in the aforementioned method of preparing a library of document D4.

6. Document D4 teaches the use of a pre-immunised source in the passage of page 9 (see lines 25 to 26) which reads: "In a preferred embodiment of the invention, the library is prepared from cells from an animal previously immunized against a determined antigen." (emphasis added by the board). Of course, the skilled person would have interpreted that statement as a direct invitation to use as a mRNA source antibody producing cells from a previously immunised animal, the choice of which is repeated at the bottom on page 9 (see line 49). However, this being a preferred form of execution and not an absolute requirement, the skilled
person would not have excluded \textit{a priori} the possibility of trying the use of cells from a non-immunised camelid as a source of mRNA. This would have been regarded by the skilled person as being a possibility having a reasonable expectation of success, especially in view of the sentence found on page 9, line 42, which reads "The preparation of antibodies \textit{can also} be performed \textbf{without a previous immunization} of Camelids" (emphasis added by the Board).

7. The appellants have argued that the aforementioned sentence found on page 9, line 42 of document D4 is to be read in strict relation with the preceding paragraph which discusses preparation of a monoclonal monoclonal antibody based on the hybridoma technology. This can clearly not be the case as that technology basically involves fusion of an immortal cell (a myeloma tumour cell) with a specific predetermined antibody-producing B cell from \textbf{immunised} animals or humans. In reality, that sentence is to be interpreted in the context of a process for the preparation of antibodies initiated by the preparation of a library of acid nucleic sequences as referred to on pages 8 and 9 (as discussed at point 3, \textit{supra}) within the frame of an \textit{in vitro} strategy such as phage display.

8. A further argument of the appellants has been that it would have been unpredictable for the skilled person that a library as prepared by the claimed method from a non-immunised source allows the preparation of high affinity antibodies. It is noted that in the experiments of the application at issue the affinity of the antibodies or fragments thereof has not been measured, so that such an advantage is not apparent but
purely hypothetical. Therefore, the argument is untenable.

9. Moreover, it is the further view of the board that, contrary to the submissions by the appellants, no relevant teaching can be derived from document D5 which could have taken the skilled person away from the preparation of a library of nucleic acid sequences with the provision of a repertoire of mRNA from a non-immunised source. Indeed, document D5 as already mentioned (see point 3, *supra*) focuses on the preparation by phage display of human antibodies, i.e. of antibodies from which the camelid heavy-chain immunoglobulins differ fundamentally as the latter have undergone extensive maturation *in vivo* which have led them to function in absence of light-chains. Such immunoglobulins are ignored in document D5.

10. Therefore, in the board's judgment, already on the basis of document D4, the method of claim 4 does not involve an inventive step. The rationale applies for obvious reasons to the library which is obtained by such a method (claims 1 to 3). Thus, the only request on file does not comply with Article 56 EPC and as such cannot form a basis for the grant of a patent.
Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:                        The Chairman:

A. Wolinski                          L. Galligani