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**Datasheet for the decision
of 16 May 2017**

Case Number: T 1705/13 - 3.3.04
Application Number: 04758448.7
Publication Number: 1615946
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C07K16/44, C12Q1/70, C12N5/06
Language of the proceedings: EN

Title of invention:
Proteolytic and covalent antibodies

Applicant:
Paul, Sudhir
Nishiyama, Yasuhiro

Headword:
Proteolytic antibodies/SUDHIR AND YASUHIRO

Relevant legal provisions:
EPC Art. 123(2), 54, 87, 88, 89, 111(1)

Keyword:
Main request - novelty (no)
Auxiliary request - novelty (yes)
Appeal decision - remittal to the department of first instance
(yes)

Decisions cited:

G 0001/15

Catchword:



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Case Number: T 1705/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 May 2017

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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted on 1 March 2013 refusing European patent application No. 04758448.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: R. Morawetz
P. de Heij

Summary of Facts and Submissions

- I. The appeal of the applicants (hereinafter "appellants") lies against the decision of the examining division refusing European patent application No. 04 758 448.7.
- II. The application at issue has the title "*Proteolytic and covalent antibodies*" and claims priority of US application No. 60/458,063, filed on 26 March 2003 (hereinafter "P1") and US application No. 60/534,689, filed on 8 January 2004 (hereinafter "P2").
- III. The following documents are referred to in this decision:
- D7 Planque S. *et al.*, Journal of Biological Chemistry (31 March 2003), vol. 278, pages 20436 to 20443.
- D8 Nishiyama Y. *et al.*, Journal of Biological Chemistry (15 December 2003), vol. 279, pages 7877 to 7883.
- D11 Paul, S. *et al.*, Journal of Biological Chemistry (28 March 2003), vol. 278, pages 20429 to 20435.
- D15 Nishiyama Y. *et al.*, Archives of Biochemistry and Biophysics (2002), vol. 402, pages 281 to 288.
- IV. The examining division held that the subject-matter of claim 11 of the main request before it failed to comply with the requirements of Article 123(2) EPC (see decision under appeal, point 3.1), that the subject-matter of claim 9 was excluded from patentability

pursuant to Article 53(c) EPC (*ibid.*, point 6), that claim 1 lacked clarity due to the use of the term "covalent antibody" and that claim 7 lacked clarity and should be reformulated to read "*for use in a method of stimulating*" (*ibid.*, point 7). It further held that the subject-matter of the claims of the main request before it was not entitled to the priority of P1 and that documents D7, D8 and D11 were thus state of the art (*ibid.*, point 4). Document D7 was considered to anticipate the subject-matter of claims 1 to 5, 8, and 10, while documents D8 and D11 were considered to anticipate the subject-matter of claims 1 to 5, 8, 10 and 11 of the main request (*ibid.*, point 8). The subject-matter of auxiliary request 1 was considered to extend beyond the application as filed (*ibid.*, point 10), while for auxiliary request 2 the requirements of Article 123(2) EPC were considered to be fulfilled while otherwise the same objections as for the main request were raised (*ibid.*, points 15 to 21). In an *obiter dictum* the examining division commented on the inventive step of the claimed subject-matter.

- V. With their statement of grounds of appeal the appellants filed a main request and auxiliary requests I to III.

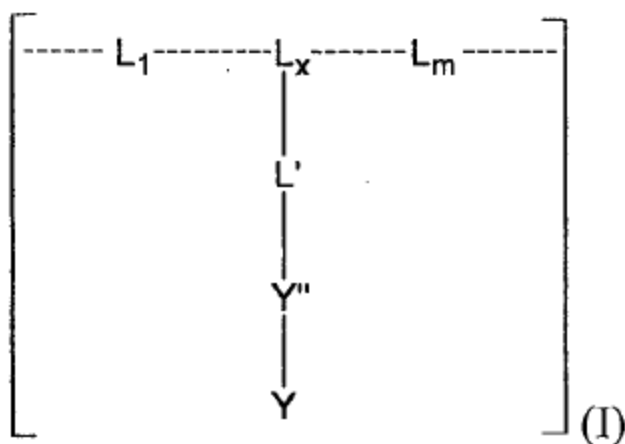
- VI. The appellants were summoned for oral proceedings and subsequently informed of the board's preliminary opinion in a communication under Article 15(1) RPBA. Document D15 was introduced into the proceedings by the board.

- VII. In response, the appellants withdrew the pending claim requests and filed a new main request and auxiliary requests I to IV.

VIII. At the oral proceedings before the board the appellants replaced their pending main request with a new main request, filed a new auxiliary request and withdrew pending auxiliary requests I to IV.

Claim 1 of the new main request reads:

"1. A method of preparing antibodies that bind covalently to a polypeptide or bind covalently and proteolytically cleave said polypeptide, the method comprising isolating the antibodies from an *ex vivo* sample obtained from an organism using a covalently reactive polypeptide analogue (pCRA) comprising an antigenic determinant of formula (I):



wherein:

L₁... L_x... L_m are, together, 4-30 amino acid components of said antigenic determinant of said polypeptide,

L_x is an amino acid determinant which is not a terminal amino acid,

L' is a side-chain functional group of L_x,

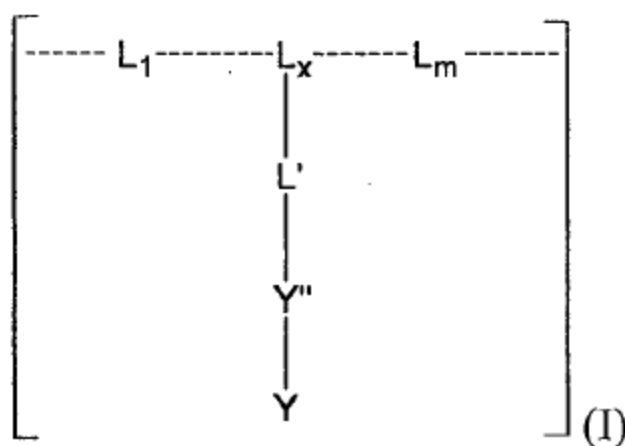
Y" is atom, covalent bond or flexible linker,

Y is a covalently reactive electrophilic group that reacts with said antibodies, and wherein the covalently

reactive electrophilic group is located in an amino acid side-chain of the antigenic determinant."

Claim 1 of the auxiliary request reads:

1. "A method of preparing antibodies that bind covalently to a polypeptide or bind covalently and proteolytically cleave said polypeptide, the method comprising isolating the antibodies from an *ex vivo* sample obtained from an organism which was previously immunized using a covalently reactive polypeptide analogue (pCRA) comprising an antigenic determinant of formula (I):



wherein:

L₁... L_x... L_m are, together, 4-30 amino acid components of said antigenic determinant of said polypeptide,

L_x is an amino acid determinant which is not a terminal amino acid,

L' is a side-chain functional group of L_x,

Y'' is atom, covalent bond or flexible linker,

Y is a covalently reactive electrophilic group that

reacts with said antibodies, and wherein the covalently reactive electrophilic group is located in an amino acid side-chain of the antigenic determinant."

Claims 2 to 4 of the auxiliary request are dependent on claim 1.

Claim 9 of the auxiliary request reads:

"9. The composition according to claim 8 for use as a medicament wherein the medical disorder is an infectious disease, HIV, a cancer, or an autoimmune disease."

At the end of the oral proceedings the chairwoman announced the board's decision.

IX. The arguments of the appellants submitted in writing and during the oral proceedings and relevant for the present decision may be summarised as follows:

Main request

Claim construction - claim 1

In the context of the method of claim 1 the feature "*isolating the antibodies from an ex vivo sample obtained from an organism using a covalently reactive polypeptide analogue (pCRA)*" covered any possible use of the pCRA to isolate the antibodies, including incubating the ex vivo sample with the pCRA and isolation of the resulting complex from the other antibodies in the sample.

Amendments (Article 123(2) EPC) - claim 1

The subject-matter of claim 1 found basis in the application as filed on page 25, lines 9 to 14 in combination with claim 1 and page 22, line 30 to page 23, line 8.

Priority (Articles 87 to 89 EPC) - claim 1

The claims of P1 in combination with the legend of Figure 7a and the example disclosed directly and unambiguously the subject-matter of claim 1. In P1, pCRA was used to identify the hybridomas that produced the antibodies, see the second paragraph on page 6. Electrophoresis of antibody-CRA complexes was disclosed on page 7, second paragraph of P1. As P1 provided a basis for the wording of claim 1 it did not need to disclose all embodiments falling within the scope of claim 1 of the main request to give rise to a right of priority.

Novelty (Article 54 EPC) - claim 1

Document D7 was not novelty-destroying because the subject-matter of claim 1 was entitled to priority from P1.

Auxiliary request

Amendments (Article 123(2) EPC) - claims 1 to 4 and 9

Basis for the subject-matter of claims 1 to 4 and 9 was provided in the application as filed on page 4, lines 10 to 25, in combination with the disclosure in the examples and the claims.

Priority (Articles 87 to 89 EPC) - claims 1 to 4 and 9

That part of the subject-matter of claims 1 to 4 and 9 that was disclosed in document D11 was entitled to priority from P1.

Novelty (Article 54 EPC) - claims 1 to 4, 9 and 10

The method according to claim 1 differed from the method disclosed in document D7 in that pCRA was used for immunisation. Document D7 did not disclose any medical use of the pCRA.

In document D8 the pCRA was used to inactivate catalytic antibodies, not to isolate them. The antibodies targeted in document D8 were not known to be involved in any kind of pathology, accordingly no medical use was disclosed in document D8.

As the pCRA disclosed in document D15 did not have an electrophilic group it did not fall within the scope of claim 10.

- X. The appellants requested that the decision under appeal be set aside and a patent be granted on the basis of the set of claims of the main request or, alternatively, on the set of claims of the auxiliary request.

Reasons for the Decision

The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Main request

Claim construction - claim 1

1. The method according to claim 1 comprises the step of "*isolating the antibodies from an ex vivo sample obtained from an organism using a covalently reactive polypeptide analogue (pCRA)*". This step is understood to encompass *inter alia* the use of the pCRA in the screening of hybridoma supernatants but also the use of the pCRA to isolate antibodies directly from the *ex vivo* sample by forming pCRA-antibody adducts, see also the application as filed on page 4, lines 23 to 26, page 25, lines 9 to 15, and page 51, line 32 to page 52, lines 9 and claims 1, 11, and 12.

Article 123(2) EPC - claim 1

2. The board is satisfied that the subject-matter of claim 1 finds basis in the application as filed on page 4, lines 10 to 23, in combination with the disclosure on page 25, lines 9 to 14, and on page 22, line 30, to page 23, line 8, and claim 1.

Priority (Articles 87 to 89 EPC) - claim 1

3. P1 discloses a method of preparing antibodies that bind covalently to a polypeptide (see page 6, second paragraph, to page 10, first paragraph, legend of Fig. 7A on page 22, claims 1, 7). A pCRA comprising an antigenic determinant of formula (I) as defined in

present claim 1 is disclosed in P1 on page 22, second paragraph in combination with the formula depicted in claim 1 of P1. According to P1 the antibodies are isolated by generating hybridomas, screening of the supernatants from the hybridoma wells for SDS-resistant binding to CRA and identification of wells secreting the desired Abs. Following cloning of the cells by limiting dilution, monoclonal IgG is purified. Irreversible binding of biotinylated CRAs by purified IgG is determined by denaturing electrophoresis.

4. P1 thus discloses one specific method for preparing antibodies that bind covalently to a polypeptide which comprises isolating antibodies from an *ex vivo* sample obtained from an organism using a pCRA, i.e. the method used in the example of P1 which involves the use of pCRA in the screening of hybridoma supernatants.
5. The appellants submitted that P1 also disclosed electrophoresis on page 7 and that the subject-matter of claim 1 was thus also entitled to priority for embodiments involving electrophoresis.
6. The board found this argument not persuasive. According to P1, electrophoresis is not used for isolating the antibodies from the *ex vivo* sample but for determining irreversible binding of CRA to the antibodies (see point 3).
7. The appellants further submitted that it was not necessary for P1 to disclose all embodiments falling within the scope of claim 1 as long as P1 provided a basis for the wording of claim 1.
8. Given the interpretation of claim 1 (see point 1) and the disclosure in P1 (see point 4) the board considers

however that the subject-matter of claim 1 relates to a generalisation compared to the invention disclosed in P1. The embodiment disclosed in P1 is encompassed, albeit without being spelt out, in the method of claim 1.

9. The subject-matter of claim 1 can thus be conceptually divided into two parts. The first part corresponding to the invention disclosed directly and unambiguously in P1 (see point 4) and entitled to priority from P1, the second part being the remaining subject-matter of claim 1, which is not entitled to the priority of P1 and which encompasses embodiments that involve the use of pCRAs to isolate antibodies, wherein the antibodies form adducts with the pCRAs, which are then isolated from the *ex vivo* sample (see point 1), see also decision of the Enlarged Board of Appeal G 1/15 of 29 November 2016, in particular points 5.1.2, 5.1.3 and 6.4.

Novelty (Article 54) - claim 1

10. Document D7 belongs to the state of the art pursuant to Article 54(2) EPC for that part of the subject-matter of claim 1 which is not entitled to the priority of P1 (see point 9).
11. Document D7 discloses the preparation of antibodies that bind covalently to the extracellular domain of human epidermal growth factor receptor (exEGFR) protein by immunising mice with exEGFR and then isolating antibodies from immune sera by using a covalently reactive antigen analog of exEGFR, namely CRA IV, to form adducts with the antibodies. That the antibodies bind covalently to CRA IV is shown by denaturing electrophoresis (see page 20 437, left-hand column,

third paragraph; page 20 439, right-hand column, last paragraph to page 20 441, left-hand column, first paragraph; Figures 5 and 6). CRA IV consists of exEGFR which presents diverse antigenic epitopes derivatised at Lys side chains with a phosphonate diester (see Fig. 1C). Therefore, document D7 is considered to disclose a method of preparing antibodies that bind covalently to a polypeptide which method falls within the scope of claim 1. This was not disputed by the appellants.

12. Therefore, the board concludes that the disclosure of document D7 anticipates the subject-matter of claim 1 of the main request, which thus fails the requirements of Article 54(2) EPC.

Auxiliary request

13. The present auxiliary request does not include claims 1, 8 and 11 of the main request before the examining division. The claims that correspond to claims 2 to 5, and 10 of said main request are claims 1 to 4 and 9 of the auxiliary request.

Article 123(2) EPC - claims 1 to 4 and 9

14. The board is satisfied that the subject-matter of claims 1 to 4 and 9 finds a basis in the application as filed on page 4, lines 10 to 25, in combination with the disclosure on page 25, lines 9 to 14, and on page 22, line 30, to page 23, line 8, Example II and claims 1, 11, and 12.

Priority (Articles 87 to 89 EPC)- claims 1 to 4 and 9

15. The examining division held that the subject-matter of the main request before it was not entitled to the priority of P1 and that documents D7, D8 and D11 thus belonged to the state of the art for the claimed subject-matter (see decision under appeal, points 4.3 to 4.3.8). It further held that document D7 anticipated the subject-matter of claims 1 to 5, 8 and 10, while documents D8 and D11 were considered to anticipate the subject-matter of claims 1 to 5, 8, 10 and 11 of the main request before it then (see decision under appeal, points 8 to 8.3).
16. The board considers, in line with decision G 1/15, *supra*, that the subject-matter of claims 1 to 4 and 9 of the auxiliary request enjoys partial priority for that part of its subject-matter that is directly and unambiguously disclosed in P1.
17. Document D11 (see abstract, page 20 429, left-hand column, first paragraph, to page 20 435, right-hand column, second paragraph) is the scientific publication corresponding to P1 (see page 1 to 21, claims, figures). In the board's judgement, the disclosure of document D11 does not extend beyond the content of P1.
18. It follows that document D11 does not belong to the state of the art pursuant to Article 54(2) EPC for that part of the subject-matter of claims 1 to 4 and 9 that is entitled to the priority of P1.
19. Since neither document D7 nor document D8 are considered to disclose subject-matter falling within the scope of claims 1 to 4 and 9 of the auxiliary request (see below, points 20 to 22), it need not be

decided for the purpose of this decision whether or not the subject-matter of claims 1 to 4 and 9 is entitled to P1 with regard to that prior art.

Novelty (Article 54 EPC) - claims 1 to 4, 9 and 10

20. The method disclosed in document D7 differs from the method of claim 1 in that the pCRA is not used for immunisation (see above point 11). Accordingly, document D7 does not anticipate the subject-matter of claim 1 or of its dependent claims 2 to 4. Since document D7 does not disclose any medical use of the pCRA it does not disclose the subject-matter of claim 9 either.
21. Document D8 reports the selective inactivation of proteolytic antibodies to an autoantigen, the neuropeptide vasoactive intestinal peptide (VIP), by a covalently reactive analog (CRA) of VIP, termed VIP-CRA (see compound 3 in Fig. 1A). The VIP-CRA is bound irreversibly by a monoclonal antibody (mAb) that catalyses the hydrolysis of VIP (see abstract). This antibody, mAb c23.5, was raised by hyper-immunisation with VIP not with pCRA (see page 7878, right-hand column, last paragraph). Therefore, document D8 does not anticipate the subject-matter of claim 1 or of its dependent claims 2 to 4. Since document D8 does not disclose any medical use of the pCRA it does not disclose the subject-matter of claim 9 either.
22. The board concludes that the subject-matter of claims 1 to 4 and 9 is not anticipated by the disclosure of documents D7 and D8.
23. Document D15 had been introduced by the board into the proceedings. The pCRA it discloses differs from the

structure of the pCRA in claim 10 of the auxiliary request in that the electrophilic group is not reactive, see page 284, top left. The subject-matter of claim 10 is thus not anticipated by the disclosure of document D15.

Allowability of the appeal

24. In the board's judgement none of the further objections raised in the decision under appeal (under Articles 123(2), 53(c) and 84 EPC, see section IV) apply to the claims of the auxiliary request as the subject-matter objected to has been either amended or deleted.
25. The appeal is thus found to be allowable.

Remittal (Article 111(1) EPC)

26. Pursuant to Article 111(1) EPC, following the examination as to the allowability of the appeal, the board will decide on the appeal and, in this respect, it may either exercise any power within the competence of the department which was responsible for the decision or remit the case for further prosecution.
27. In a case such as the present one, where the examining division has dealt with inventive step only in the form of an *obiter dictum* and with the requirements of Article 83 EPC not at all, the board, exercising its discretion under Article 111(1), second sentence, EPC, decides to remit the case to the examining division for further prosecution, thereby giving the appellants the possibility of having their case heard by two instances.

28. The case is accordingly remitted to the examining division for further prosecution on the basis of the claims of the auxiliary request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution on the basis of the set of claims of the auxiliary request filed at the oral proceedings at 17:45 hrs.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated