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Datasheet for the decision of 16 November 2021

Case Number: T 2589/16 - 3.3.04

Application Number: 08735001.3

Publication Number: 2155783

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Language of the proceedings: EN

Title of invention:

Cross-species-specific CD3-epsilon binding domain

Patent Proprietor:

Amgen Research (Munich) GmbH

Opponents:

Janssen Biotech, Inc.
F.Hoffmann-La Roche AG
Engmab AG
Genmab A/S
Affimed GmbH (opposition withdrawn)
Chugai Seiyaku Kabushiki Kaisha
Pfizer Inc.

Headword:
Cross-species CD3 antibody/AMGEN

Relevant legal provisions:
EPC Art. 56, 83, 87, 123(2)
RPBA Art. 12(4), 13(1)

Keyword:
Late-filed main request and auxiliary requests 20A, 20B, 20C, 20D
Late-filed auxiliary requests - admitted (no)
Auxiliary request 21 - Priority - same invention (yes); Amendments - allowable (yes); Sufficiency of disclosure - (yes); Inventive step - (yes)
Late-filed objection - submitted during oral proceedings - admitted (no) - inadequately substantiated - admitted (no)

Decisions cited:
T 2221/10, T 0197/10

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2589/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 November 2021

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Respondent: (Opponent 7)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 October 2016 concerning maintenance of the European Patent No. 2155783 in amended form**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	M. Blasi

Summary of Facts and Submissions

I. The patent proprietor and opponents 1 to 4 filed appeals against the decision of the opposition division that, account being taken of the amendments in the form of auxiliary request 18, European patent No. 2 155 783 and the invention to which it related met the requirements of the EPC. The patent, entitled "*Cross-species-specific CD3-epsilon binding domain*", had been granted on European patent application No. 08 735 001.3, which was filed as an international application under the PCT, published as WO 2008/119567 (the "application as filed"). It claimed priority from European patent application Nos. 07 006 990.1 (P1), 07 006 988.5 (P2) and 08 004 741.8 (P4) and US patent application 60/931,688 (P3).

II. Originally, seven parties had filed oppositions.

Opponent 5 withdrew the opposition during the appeal proceedings. Since no issues other than substantive issues arose in this appeal, opponent 5 ceased to be a party to the appeal proceedings.

Opponents 6 and 7 are respondents in these proceedings.

For ease of reference, in this decision the board refers to the parties as patent proprietor and opponents 1 to 7 or "appellants-opponents" when referring to opponents 1 to 4.

III. The patent was opposed as a whole under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC), lack of inventive step

(Article 56 EPC) and lack of industrial applicability (Article 57 EPC), and under Article 100(b) and (c) EPC.

IV. In the decision under appeal, the opposition division dealt with a main request (the patent as granted) and 18 auxiliary requests. It held, *inter alia*, with respect to the main request, that the subject-matter claimed did not extend beyond the content of the application as filed but that the subject-matter of some claims lacked novelty in view of the disclosure of document D6, which was prior art in accordance with Article 54(3) EPC; with respect to the set of claims of auxiliary request 18, it held that the subject-matter was entitled to the earliest priority date claimed, thus excluding document D6 as prior art under Article 54(2) EPC, and that the claimed invention was sufficiently disclosed and involved an inventive step with regard to document D3 as representing the closest prior art.

V. With the statement of grounds of appeal, the patent proprietor filed sets of claims of a main request and 21 auxiliary requests and several new documents. Auxiliary request 21 is identical to auxiliary request 18 considered allowable by the opposition division.

VI. The appellant-opponents filed statements of grounds of appeal, some of them including new documents.

VII. The patent proprietor and opponents 1 to 7 submitted replies to the statements of grounds of appeal.

VIII. Opponent 4 subsequently filed a further submission.

With the letter dated 11 July 2019, opponent 2 filed a further submission, accompanied by decision T 628/15.

IX. By letter dated 4 September 2019, the patent proprietor submitted sets of claims of further auxiliary requests 16A, 18A, 19A, 20A, 20B, 20C, 20D, 22 to 25, 22A to 25A and 25B.

X. The board appointed oral proceedings in view of corresponding requests of the parties.

XI. Opponents 1 and 6 subsequently filed one further submission each.

XII. By letter dated 4 March 2020, the patent proprietor filed sets of claims of auxiliary requests 22-R, 22A-R, 23-R, 23A-R, 24-R and 24A-R.

XIII. In a communication pursuant to Article 15(1) RPBA 2020 dated 26 October 2020, the board took note of the parties' requests submitted in writing, including the withdrawal of auxiliary requests 1 to 19, 16A, 18A, 19A, 25, 25A and 25B, and informed the parties of its preliminary opinion, *inter alia,* that document D6 disclosed embodiments encompassed by claim 1 of the main request.

XIV. Subsequently, one further substantive submission was filed by the patent proprietor indicating, *inter alia,* a new hierarchy of the claim requests.

XV. Further submissions were also filed by opponents 1, 2, 4, 6 and 7.

XVI. After several postponements, *inter alia* due to the COVID-19 pandemic, the oral proceedings took place on

15 and 16 November 2021 as an in-person hearing. All parties to the appeal proceedings attended the oral proceedings.

At the beginning of the oral proceedings, the patent proprietor withdrew the main request filed with the statement of grounds of appeal and stated that auxiliary request 20 was the new main request.

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

XVII. The following claim requests were considered at the oral proceedings: main request (filed as auxiliary request 20 with the statement of grounds of appeal), and auxiliary requests 20A, 20B, 20C, 20D (all filed with the letter dated 4 September 2019) and 21 (filed with the statement of grounds of appeal; being the same as the request held by the opposition division to comply with the requirements of the EPC).

XVIII. Claims 1, 3 and 4 of the main request read:

"1. A polypeptide comprising a binding domain which is an antibody capable of binding to an epitope of human and Callithrix jacchus, Saguinus oedipus or Saimiri sciureus CD3ε chain, wherein the epitope is part of an amino acid sequence comprised in the group consisting of SEQ ID NOs:2, 4, 6, or 8 and comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu, wherein the antibody is a scFv, wherein said scFv does not comprise CDR-L1 having the sequence RSSTGAVTTSNYAN, CDR-L2 having the sequence GTNKRAP, and CDR-L3 having the sequence ALWYSNLWV and CDR-H1 having the sequence TYAMN, CDR-H2 having the sequence RIRSKYNNYATYYADSVKD and CDR-H3 having the sequence HGNFGNSYVSWFAY or

CDR-H3* comprising the amino acid sequence "VSWFAY", and wherein the polypeptide further comprises a second binding domain capable of binding to a cell surface antigen which is a tumor antigen.

3. A polypeptide comprising a binding domain which is an antibody capable of binding to an epitope of human and Callithrix jacchus, Saguinus oedipus or Saimiri sciureus CD3ε chain, wherein the epitope is part of an amino acid sequence comprised in the group consisting of SEQ ID NOs:2, 4, 6, or 8 and comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu, wherein the antibody is a scFv or a single domain antibody, wherein the first binding domain comprises a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from:

(a) CDR-L1 as depicted in SEQ ID NO:27, CDR-L2 as depicted in SEQ ID NO:28 and CDR-L3 as depicted in SEQ ID NO:29;

(b) CDR-L1 as depicted in SEQ ID NO:117, CDR-L2 as depicted in SEQ ID NO:118 and CDR-L3 as depicted in SEQ ID NO:119; and

(c) CDR-L1 as depicted in SEQ ID NO:153, CDR-L2 as depicted in SEQ ID NO:154 and CDR-L3 as depicted in SEQ ID NO:155,

and wherein the polypeptide further comprises a second binding domain capable of binding to a cell surface antigen which is a tumor antigen.

4. A polypeptide comprising a binding domain which is an antibody capable of binding to an epitope of human and Callithrix jacchus, Saguinus oedipus or Saimiri sciureus CD3ε chain, wherein the epitope is part of an

amino acid sequence comprised in the group consisting of SEQ ID NOs:2, 4, 6, or 8 and comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu, wherein the antibody is a scFv or a single domain antibody, wherein the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 selected from:

(a) CDR-H1 as depicted in SEQ ID NO:12, CDR-H2 as depicted in SEQ ID NO:13 and CDR-H3 as depicted in SEQ ID NO:14;

(b) CDR-H1 as depicted in SEQ ID NO:30, CDR-H2 as depicted in SEQ ID NO:31 and CDR-H3 as depicted in SEQ ID NO:32;

(c) CDR-H1 as depicted in SEQ ID NO:48, CDR-H2 as depicted in SEQ ID NO:49 and CDR-H3 as depicted in SEQ ID NO:50;

(d) CDR-H1 as depicted in SEQ ID NO:66, CDR-H2 as depicted in SEQ ID NO:67 and CDR-H3 as depicted in SEQ ID NO:68;

(e) CDR-H1 as depicted in SEQ ID NO:84, CDR-H2 as depicted in SEQ ID NO:85 and CDR-H3 as depicted in SEQ ID NO:86;

(f) CDR-H1 as depicted in SEQ ID NO:102, CDR-H2 as depicted in SEQ ID NO:103 and CDR-H3 as depicted in SEQ ID NO:104;

(g) CDR-H1 as depicted in SEQ ID NO:120, CDR-H2 as depicted in SEQ ID NO:121 and CDR-H3 as depicted in SEQ ID NO:122;

(h) CDR-H1 as depicted in SEQ ID NO:138, CDR-H2 as depicted in SEQ ID NO:139 and CDR-H3 as depicted in SEQ ID NO:140;

(i) CDR-H1 as depicted in SEQ ID NO:156, CDR-H2 as depicted in SEQ ID NO:157 and CDR-H3 as depicted in SEQ ID NO:158; and

(j) CDR-H1 as depicted in SEQ ID NO:174, CDR-H2 as depicted in SEQ ID NO:175 and CDR-H3 as depicted in SEQ ID NO:176,

and wherein the polypeptide further comprises a second binding domain capable of binding to a cell surface antigen which is a tumor antigen."

XIX. Claim 1 of auxiliary request 20A reads (additions as compared to the main request highlighted by the board by underlining)(claims 3 and 4 remained unamended):

"1. A pharmaceutical composition comprising a polypeptide comprising a binding domain which is an antibody capable of [...]"

XX. Claim 1 of auxiliary request 20B reads (differences to the main request highlighted by the board using underlining for additions and strike-through for deletions)(claims 3 and 4 remained unamended):

"1. A pharmaceutical composition comprising a polypeptide comprising a binding domain which is an antibody capable of [...] wherein said scFv does not comprise CDR-L1 having the sequence RSSTGAVTTSNYAN, CDR-L2 having the sequence GTNKRAP, and CDR-L3 having the sequence ALWYSNLWV and CDR-H1 having the sequence TYAMN, CDR-H2 having the sequence RIRSKYNNYATYYADSVKD

and ~~CDR-H3 having the sequence HGNFGNSYVSWFAY or~~ CDR-H3* comprising the amino acid sequence "VSWFAY", [...]"

XXI. Claim 1 of auxiliary request 20C reads (differences to the main request highlighted by the board using underlining for additions and strike-through for deletions)(claims 3 and 4 remained unamended):

"1. A pharmaceutical composition comprising a polypeptide comprising a binding domain which is an antibody capable of [...] wherein said scFv does not comprise CDR-L1 having the sequence RSSTGAVTTSNYAN, CDR-L2 having the sequence GTNKRAP, and CDR-L3 having the sequence ALWYSNLWV and CDR-H1 having the sequence TYAMN, CDR-H2 having the sequence RIRSKYNNYATYYADSVKD and CDR-H3 having the sequence HGNFGNSYVSWFAY ~~or CDR-H3* comprising the amino acid sequence "VSWFAY"~~, [...]"

XXII. The set of claims of auxiliary request 20D corresponds to that of the main request where claims 1 and 2 were deleted and claims 3 and 4 were renumbered to claims 1 and 2, respectively.

XXIII. Claim 1 of auxiliary request 21 reads:

"1. A polypeptide comprising a binding domain which is an antibody capable of binding to an epitope of human and Callithrix jacchus, Saguinus oedipus or Saimiri sciureus CD3ε chain, wherein the epitope is part of an amino acid sequence comprised in the group consisting of SEQ ID NOs: 2, 4, 6, or 8 and comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu, wherein the polypeptide further comprises a second binding domain capable of binding to a cell surface antigen which is a

tumor antigen, wherein the first binding domain comprises a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from:

(a) CDR-L1 as depicted in SEQ ID NO:27, CDR-L2 as depicted in SEQ ID NO:28 and CDR-L3 as depicted in SEQ ID NO:29;
(b) CDR-L1 as depicted in SEQ ID NO:117, CDR-L2 as depicted in SEQ ID NO:118 and CDR-L3 as depicted in SEQ ID NO:119; and
(c) CDR-L1 as depicted in SEQ ID NO:153, CDR-L2 as depicted in SEQ ID NO:154 and CDR-L3 as depicted in SEQ ID NO:155; and

comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 selected from:

(a) CDR-H1 as depicted in SEQ ID NO:12, CDR-H2 as depicted in SEQ ID NO:13 and CDR-H3 as depicted in SEQ ID NO:14;
(b) CDR-H1 as depicted in SEQ ID NO:30, CDR-H2 as depicted in SEQ ID NO:31 and CDR-H3 as depicted in SEQ ID NO:32;
(c) CDR-H1 as depicted in SEQ ID NO:48, CDR-H2 as depicted in SEQ ID NO:49 and CDR-H3 as depicted in SEQ ID NO:50;
(d) CDR-H1 as depicted in SEQ ID NO:66, CDR-H2 as depicted in SEQ ID NO:67 and CDR-H3 as depicted in SEQ ID NO:68;
(e) CDR-H1 as depicted in SEQ ID NO:84, CDR-H2 as depicted in SEQ ID NO:85 and CDR-H3 as depicted in SEQ ID NO:86;
(f) CDR-H1 as depicted in SEQ ID NO:102, CDR-H2 as depicted in SEQ ID NO:103 and CDR-H3 as depicted in SEQ ID NO:104;

(g) CDR-H1 as depicted in SEQ ID NO:120, CDR-H2 as depicted in SEQ ID NO:121 and CDR-H3 as depicted in SEQ ID NO:122;
(h) CDR-H1 as depicted in SEQ ID NO:138, CDR-H2 as depicted in SEQ ID NO:139 and CDR-H3 as depicted in SEQ ID NO:140;
(i) CDR-H1 as depicted in SEQ ID NO:156, CDR-H2 as depicted in SEQ ID NO:157 and CDR-H3 as depicted in SEQ ID NO:158; and
(j) CDR-H1 as depicted in SEQ ID NO:174, CDR-H2 as depicted in SEQ ID NO:175 and CDR-H3 as depicted in SEQ ID NO:176."

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

D3: WO 2005/061547

D6: WO 2007/042261

D11: Kontermann R.E., Acta Pharmacologica Sinica 26(1), 2005, pp. 1-9

D18a: Experimental results - SP34 binding experiments prepared by opponent 2

D19: Experimental report on SP34 binding prepared by opponent 1

D39: Archived webpage from 7 September 2006 - Beth Israel Deaconess Medical Center

D48: WO 2000/041474

D50: Schlereth B. *et al.*, Cancer Research 65(7), 2005, pp. 2882-2889

D52a: Results of alanine-scanning experiment of the terminal 27 amino acids of CD3 epsilon using SP34, A2J and H2C, filed by opponent 2 during opposition proceedings

D101: Experimental report "CD3 epsilon epitope mapping" filed on 21 March 2016 by opponent 2

D103: Experimental report "Cytokine secretion data I and II" filed on 27 April 2016 by the patent proprietor

D112: Experimental report "Epitope mapping of A2J, E2M, H2C, F12Q, H1E, F7O, I2C, F6A, G4H antibodies" dated 28 February 2017 filed by the patent proprietor

XXV. Further documents filed in this appeal proceedings are not referred to in this decision because they were filed either in relation to an issue which the board need not decide or in relation to an issue decided in favour of the party filing them without the need for the board to take them into account.

XXVI. The arguments of the patent proprietor, in so far as relevant to this decision, may be summarised as follows.

Main request
Admittance into the appeal proceedings
(Article 12(4) RPBA 2007)

This claim request had been filed with the statement of grounds of appeal and had thus been long in the procedure. It was based on auxiliary request 15 considered in the decision under appeal.

The deletion of the alternative "single domain antibody" from claim 1 constituted a simplification.

The word "having" used in the definition of the CDRs meant "consisting". This meaning was used for example in document D6. This amendment aimed at providing a self-contained claim.

Auxiliary request 20A
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

This claim request was filed in reaction to the filing by opponent 2, with the letter dated 11 July 2019, of decision T 628/15 of the current board concerning, allegedly, closely related subject-matter. The decision dealt with the issue of Article 123(2) EPC with respect to a claim defining a combination of light chain and heavy chain CDRs.

By the addition of the expression "a pharmaceutical composition comprising", the claim now had the format of a purpose-limited product claim according to Article 54(4) EPC.

Auxiliary requests 20B and C
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

These claim requests were filed in reaction to the objection put forward in opponent 6's reply to the appeal (see point 7.4.).

Auxiliary request 20D
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

This request should be admitted into the appeal proceedings as a reaction to the new objection of opponent 2 under Article 123(2) EPC raised for the first time in appeal proceedings.

Claims 1 and 2 of this request were identical to claims 4 and 5 as granted. These claims were also present in the main request as claims 3 and 4. No objections to these claims had been raised by the opponents during the opposition proceedings. Thus, the request did not add to the complexity of the case.

Auxiliary request 21 - claim 1

Amendments - Article 123(2) EPC

Admittance of an objection under Article 123(2) EPC
(Article 12(4) RPBA 2007)

The amendment during the opposition proceedings by which the sequences of the CDRs of the light and heavy variable regions were inserted into claim 1 of the then auxiliary request 18 had not been objected to during the opposition proceedings. In fact, the decision under appeal stated that no objections under Article 123(2) EPC were raised in respect of this request.

This objection constituted an amendment of the opponents' case. The objection could have been brought forward in opposition proceedings and should not be admitted in the appeal proceedings.

Further objection under Article 123(2) EPC

The epitope in claim 1 was the pentapeptide Q-D-G-N-E disclosed on page 26, line 11 of the description by the three-letter amino acid code Gln-Asp-Gly-Asn-Glu.

The application disclosed that the epitope was part of amino acid sequences having SEQ ID NOs: 2, 4, 6 and 8 (see page 26, first two paragraphs). However, from the sequence alignment provided in document D20b of the N-terminal 27 amino acids of these sequences, it was apparent that in none of those sequences the amino acid "D" followed the pentapeptide sequence Q-D-G-N-E, i.e. the pentapeptide recited in the claim. Thus, the epitope could not be the hexapeptide Q-D-G-N-E-D, i.e. the one in brackets on page 26, line 11 of the application, and the pentapeptide was the correct sequence of the epitope.

Moreover, the passage on page 8, lines 23 to 30 also disclosed the epitope with only the five amino acids.

Furthermore, it was common practice in the technical field to repeat the three-letter code sequence in abbreviated form, i.e. in the one letter code, in brackets. Therefore, that passage of the application did not disclose a list of two sequences for the epitope. Instead, the same sequence was given in a three-letter code followed by its abbreviation in a one-letter code, and no selection needed to take place.

Sufficiency of disclosure (Article 83 EPC)

Admittance of the objection of lack of sufficient disclosure into the appeal proceedings (Article 12(4) RPBA 2007)

The statement of grounds of appeal of opponent 1 (point 4.1) briefly referred to a communication of the examining division. This did not comply with the requirements for substantiation of an objection. Thus, the objection should not be admitted into the appeal proceedings.

Sufficiency of disclosure

The skilled person was aware of binding domains derived from molecules other than antibodies. An example of such a binding domain was lipocalin (letter of reply to the appeals, section B).

The opponents had not provided verifiable facts to substantiate serious doubts.

Inventive step (Article 56 EPC)

Admittance of the objection based on antibody SP34 as representing the closest prior art

No arguments were provided in this respect.

Admittance of the objection based on document D48 as representing the closest prior art

The objection raised by opponent 4 for the first time at the oral proceedings should not be admitted. This document had previously been addressed in the context

of novelty but had not been put forward as representing the closest prior art. Thus, a line of argument on inventive step starting from this disclosure had never been submitted until the oral proceedings before the board.

Moreover, no reasons had been presented why this disclosure would be closer to the claimed subject-matter than the disclosure in each of documents D3, D11 and D50.

Inventive step in view of document D6 as representing the closest prior art

Priority (Article 87 EPC)

The application as filed and the patent applications P1 and P2 disclosed the same Q-D-G-N-E epitope. Furthermore, the context-independence of the N-terminal amino acids 1 to 27 of CD3, where the epitope was located, the epitope being linked with the effect on T cell redistribution, was already disclosed in the applications P1 and P2.

Both of these priority applications disclosed binding domains binding to human and non-chimpanzee primate CD3 epsilon (P1, page 22, third full paragraph and P2, page 7, first full paragraph). The term "antibody", referring to the CD3 binding domain, included various embodiments such as chimeric and humanised antibodies, and the generation of mouse antibodies and their humanised versions was disclosed (P1, page 18 and examples 1 and 2). Thus, the subject-matter was not restricted to binding domains derived from humans.

Hence, since claim 1 validly claimed priority from P1 and P2, document D6 did not constitute prior art according to Article 54(2) EPC and could therefore not be taken to represent the closest prior-art document in the assessment of inventive step.

Inventive step in view of document D3, document D11 or document D50 as representing the closest prior art

Closest prior art and objective technical problem

The claimed bispecific polypeptide differed from that disclosed in the prior-art documents D3, D11 and D50 by the epitope to which it bound on CD3.

The binding to this epitope resulted in two technical effects: the ability of the antibody to cross-react with human and New World monkey CD3 and an increased efficacy due to reduced T cell redistribution.

Thus, the objective technical problem was to be formulated as the provision of a cross-species reactive antibody with increased efficacy in BiTE (bispecific T cell engager) therapy.

Obviousness

Even when the objective technical problem was formulated without taking into account the second effect, it was nevertheless not obvious to provide the claimed polypeptide.

Given that the binding domains of antibody SP34 already presented cross-species reactivity, there was no need to provide further cross-species reactive antibodies by modifying antibody SP34.

The skilled person would not have used antibody SP34 for providing a binding domain for CD3 for the following reasons:

(i) There was a prejudice against using cross-reactive CD3 antibodies because they would cause T cell activation and/or T cell redistribution. Thus, the skilled person would not have used antibody SP34 due to its cross-species reactivity.

(ii) If the skilled person had used a cross-species reactive antibody, the antibody SP34 would not have been the only choice since other antibodies with cross-species reactivity were known, as shown in documents D61 and D24.

(iii) Knowledge of the epitope to which SP34 bound could not be used for the assessment of inventive step as it was only determined by the opponents in knowledge of the patent or application.

Furthermore, there were alternative solutions, for example polypeptides binding to CD5 instead of CD3 or polypeptides binding to a different epitope on CD3.

It was not obvious to provide variants of the CD3 binding domains of antibody SP34. The epitope bound by SP34 was not known at the earliest date of priority claimed. Thus, it was not routine to provide such variants. There was no reasonable expectation of success; only mere hope.

Modifications to the CDRs of antibody SP34 could result in binding to a different epitope. There was no

guidance on how to arrive at the alternative CDRs in the claim.

XXVII. The arguments of the appellant-opponents and the respondents, opponent 6 and opponent 7, may be summarised as follows.

Main request
Admittance into the appeal proceedings
(Article 12(4) RPBA 2007)

This request should not be admitted into the appeal proceedings because the amended wording used to define the CDRs introduced clarity issues which had not been addressed in the decision under appeal.

Furthermore, the disclaimer did not comply with the requirements of Articles 123(2) and 84 EPC.

The request was thus not *prima facie* allowable.

The patent proprietor had not put forward any reasons why this request could not have been filed in the proceedings before the opposition division, neither had any indication been given as to which ground for opposition the request was meant to address.

Auxiliary request 20A
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

This request should not be admitted into the appeal proceedings because the claims did not fulfil the requirement of clear allowability. The issues raised in the context of the main request under Articles 123(2) and 84 EPC, arising from the amended wording "having"

in the definition of the CDRs as well as from the disclaimers, applied equally here.

The insertion of the wording "pharmaceutical composition" did not address the issues concerning the scope of the disclaimer and added to the complexity of the case.

The objection under Article 123(2) EPC had been submitted with the opponents' statements of grounds of appeal and therefore could not justify the timing of the filing of this request.

Auxiliary requests 20B and C
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

These requests should not be admitted into the appeal proceedings for the same reasons as put forward for auxiliary request 20A.

Auxiliary request 20D
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

Claim 1 of this request defined the polypeptide in terms of either the VH or the VL CDRs. Such subject-matter had not been addressed earlier in the proceedings and required considerations of the biological properties imparted to the polypeptide by the sequences of the VH or the VL regions separately, the combination no longer being required. Thus, this request should not be admitted into the appeal proceedings because it added to the complexity of the case.

Furthermore, the request constituted a reaction to the objections of lack of novelty based on document D6 which were already in the proceedings before the opposition division. Therefore, the request could and should have been filed earlier.

The objection under Article 123(2) EPC was submitted with the statements of grounds of appeal and therefore could not justify the timing of the filing of this request.

Auxiliary request 21 - claim 1

Amendments - Article 123(2) EPC

Admittance of an objection under Article 123(2) EPC (Article 12(4) RPBA 2007)

The board had discretion to admit the objection.

The objection was *prima facie* highly relevant in view of the decision in case T 628/15.

Analysing the objection involved no complexity, and the impact in terms of procedural economy was low as no documents were involved other than the patent application.

The patent proprietor had had time to react to the objection in advance of the oral proceedings.

Further objection under Article 123(2) EPC

The three species *Callithrix jacchus*, *Saguinus oedipus* and *Saimiri sciureus* constituted a selection from those

disclosed on pages 14 to 18 of the application as filed.

The peptide Gln-Asp-Gly-Asn-Glu also constituted a selection from two possibilities on page 26, line 11 of the application as filed. Thus, claim 1 included a combination of two selections.

From the passage on page 26 of the application, it was not clear whether a pentapeptide or a hexapeptide was meant.

Multiple corrections were possible for the hexapeptide. Besides the correction consisting of the deletion of the last amino acid in the hexapeptide, a possible correction would be its replacement with the amino acid E, glutamic acid. Such a hexapeptide would fall within SEQ ID NOs 2, 4, 6 and 8. Therefore, the hexapeptide could not be corrected by deletion of the last amino acid, and two possibilities were disclosed in this passage of the description.

Sufficiency of disclosure (Article 83 EPC)

The examining division in the communication of 7 February 2011 (point 6.1) had raised an objection of lack of sufficiency of disclosure for binding domains other than derived from antibodies (see statement of grounds of appeal of opponent 1, point 4.1).

Inventive step (Article 56 EPC)

Admittance of the objection based on antibody SP34 as representing the closest prior art

In opponent 4's letter of 17 March 2021 on pages 5 and 6, an objection was developed selecting as the closest prior art the commercially available antibody SP34.

No arguments were provided in relation to admittance of this objection into the appeal proceedings.

Admittance of the objection based on document D48 as representing the closest prior art

The disclosure in document D48 was addressed in opponent 1's letter dated 17 July 2017 (points 3.16 and 7.39). A reference to inventive step was made in points 3.60 and 7.10 of that letter. The claims as a whole had been objected to under inventive step. Since this included the dependent claims of the then main request, it followed that also the features of claim 1 of auxiliary request 21 had been objected to.

This document represented the closest prior art because it referred to antibody SP34, and therefore the claimed subject-matter differed from it merely in the specific CDR sequences.

Inventive step in view of document D6 as representing the closest prior art

Priority (Article 87 EPC)

Priority was not claimed in respect of the same invention as disclosed in earlier applications P1 and P2 for two reasons.

The earlier applications did not disclose that the epitope resulted in less T cell redistribution during the starting phase of the treatment, as disclosed in the application (page 6, line 24 to page 8, line 7). This effect resulted in a functional definition of the epitope in addition to the structural definition consisting of the amino acid sequence recited in the claim. The skilled person was thus presented with new information, not directly and unambiguously derivable from the earlier patent applications (see decision G 2/98).

Moreover, including the effect of T cell redistribution in the formulation of the objective technical problem was impermissible because it took into account knowledge not available at the priority date.

All the relevant passages in each of the priority applications required that the binding domain be a human binding domain (e.g. on pages 1, 6 to 11, 21, 165 and 171 of patent application P1). However, this requirement was not present in the claims. Thus, none of the claimed subject-matter was entitled to the priority date claimed from applications P1 and P2.

Hence, since priority from earlier applications P1 and P2 was not validly claimed for the subject-matter

of claim 1, document D6 constituted prior art according to Article 54(2) EPC and could therefore be taken to represent the closest prior-art document in the assessment of inventive step.

Inventive step in view of document D3, document D11 or document D50 as representing the closest prior art

Closest prior art and objective technical problem

The closest prior art could be represented by the bispecific CD3-binding molecules disclosed in each of documents D3, D11 and D50.

The claimed subject-matter differed from these by the epitope to which the polypeptides (antibodies) bound and their CDR sequences.

Binding to the particular epitope resulted in the ability of the antibody to cross-react with human and New World monkey CD3.

No effect in terms of increased efficacy of the antibody due to reduced T cell redistribution could be acknowledged, for the following reasons:

(i) The meaning of "reduced T cell redistribution" was not clear - a term which had no recognised meaning in the art should not be incorporated into the formulation of the objective technical problem.

(ii) It was not clear how to measure "reduced T cell redistribution" - in the patent, T cell counts were the property measured.

(iii) The experimental data in the patent did not unambiguously substantiate such an effect for the bispecific constructs tested - the experiments for comparing the constructs according to the claim with other constructs differed by several parameters.

(iv) If present, such an effect would inevitably be present for the antibody SP34 since, according to the patent proprietor, the effect of reducing T cell redistribution resulted from binding to the specific epitope. Since antibody SP34 bound to the same epitope, such an effect would thus be merely a bonus effect present in the obvious bispecific construct based on antibody SP34.

(v) As an alternative to the previous point, it had to be assumed that the effect was not achieved by all antibodies binding to the epitope as defined in the claim, and consequently not all constructs falling within the scope of the claim achieved this technical effect.

(vi) The experimental results provided in document D103 showed that such a technical effect could not be attributed to the epitope.

The objective technical problem was thus to be formulated as the provision of a bispecific CD3 and tumour antigen binding polypeptide which presented cross-species reactivity with human and New World monkey CD3. Alternatively, the objective technical problem could be formulated as the provision of improved CD3-binding BiTE molecules or as the provision of CD3-binding bispecific polypeptides reacting with the three species indicated in claim 1.

The objective technical problem defined by the patent proprietor, or that adopted by the opposition division, amounted to two distinct problems, one being the "cross-species reactive" problem and the other being the "reduced adverse events/reduced T cell redistribution" problem.

Should the problem be formulated with both parts, if the solution to one part had been obvious, the provision of a solution to the other part would merely have been a bonus effect.

The objective technical problem as formulated by the opposition division was not solved over the whole scope of the claim - cross-species reactivity was shown only for four antibodies, i.e. only for some of the CDR combinations covered by the claim, and T cell redistribution results were shown for only one of the antibodies. Moreover, for none of the specific antibodies in the patent were there experimental results with regard to both technical effects.

The two problems in the problem as formulated by the opposition division were in fact partial problems.

Obviousness

To provide a cross-species reactive CD3-binding bispecific polypeptide, the skilled person would have used antibody SP34 for the CD3 binding domain because it was the only CD3 antibody known to present cross-reactivity.

The CD3 binding domain in claim 1, as defined by the CDR sequences, bound to the same epitope as antibody SP34. The particular CDRs within the binding domains

claimed were mere arbitrary alternatives to the obvious CDRs within the SP34 binding domains.

The fact that the particular CDRs were not predictable in advance did not make them contribute to inventive step. No technical effect was known associated with the differences in the CDR sequences versus those in antibody SP34. Decisions T 735/00 (Reasons 26) and T 2637/11 (Reasons 20) were relevant in this context. In particular, in decision T 735/00, the board held that the preparation of antibodies was routine. Also, mutagenesis of known CDRs was routine.

The skilled person would have been motivated to provide polypeptides with cross-species reactivity and thus would have modified the prior-art bispecific polypeptides to provide them with binding domains based on antibody SP34. It was not necessary to know the epitope bound by this antibody.

Because the skilled person would have used antibody SP34, the resulting polypeptide would have bound to the same epitope as SP34, as required by the claim.

The claimed variants could easily be generated without any technical difficulties, for example by mutagenesis of the CDRs and selection for cross-reactivity. Document D48 disclosed in-vitro mutagenesis for modifying CDRs (page 9, lines 12 to 16, paragraph 3 and page 10, first paragraph). Only routine methods were involved.

Although the epitope bound by antibody SP34 was not known in the prior art, it could be determined.

Each of the multiple steps indicated by the opposition division was routine and therefore did not lead to the presence of an inventive step.

Requests of the parties relevant for the present decision

XXVIII. The patent proprietor requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request, filed as auxiliary request 20 with the statement of grounds of appeal or, alternatively, on the basis of one of the sets of claims of auxiliary requests 20A, 20B, 20C and 20D, all filed with the letter dated 4 September 2019 or, further alternatively, on the basis of the set of claims of auxiliary request 21, filed with the statement of grounds of appeal, auxiliary request 21 being identical to the version considered allowable by the opposition division, thus implying that the appeals of the opponents be dismissed.

The patent proprietor further requested that documents D110 to D112 and D120 to D122 be admitted into the proceedings.

XXIX. Appellant-opponents 1 to 4 requested that the decision under appeal be set aside and that the patent be revoked in its entirety. They also requested that the main request and all auxiliary requests except for auxiliary request 21 not be admitted into the proceedings and that all documents filed by the opponents be admitted into the proceedings.

Respondent-opponents 6 and 7 requested that the patent proprietor's appeal be dismissed.

Reasons for the Decision

1. The appeals comply with the requirements specified in Articles 106 to 108 EPC and the further provisions referred to in Rule 99 EPC and are admissible.

Applicable provisions of the Rules of Procedure of the Boards of Appeal (RPBA)

2. A revised version of the RPBA entered into force on 1 January 2020 (RPBA 2020). The revised version applies to appeals pending on the date of the entry into force, subject to transitional provisions (Article 25 RPBA).

3. In the present case, the statements of grounds of appeal, as well as the timely filed replies thereto, were filed before 1 January 2020. Thus, Article 12(4) to (6) RPBA 2020 does not apply to these submissions. Instead, Article 12(4) RPBA 2007 applies (Article 25(2) RPBA).

4. The parties were notified of the summons to oral proceedings before 1 January 2020. Thus, Article 13(2) RPBA 2020 does not apply. Instead, Article 13 RPBA 2007 applies (Article 25(3) RPBA).

Main request
Admittance into the appeal proceedings
(Article 12(4) RPBA 2007)

5. Claim 1 of the main request differs from claim 1 of auxiliary request 15 considered by the opposition division in the decision under appeal on two accounts:

(i) deletion of the alternative "single domain antibody" and (ii) replacement of each SEQ ID number by the corresponding sequence in full. Along with the replacement of the SEQ ID numbers, the wording preceding the sequences was amended, as exemplified in the following with respect to SEQ ID NO: 118 (difference underlined by the board):

"*wherein said scFv does not comprise CDR-L1 (SEQ ID NO.118)*" in auxiliary request 15

now reads

"*wherein said scFv does not comprise CDR-L1 having the sequence RSSTGAVTTSNYAN*".

6. This claim request was filed with the patent proprietor's statement of grounds of appeal. Its admittance into the appeal proceedings was contested. The opponents submitted, *inter alia,* that the new wording introduced clarity issues in view of the term "having" in the definition of the CDRs.

7. Pursuant to Article 12(4) RPBA 2007, the board has discretion to hold inadmissible facts, evidence or requests filed with the statement of grounds of appeal, *inter alia,* if they could have been presented in the proceedings before the opposition division.

8. The patent proprietor did not put forward reasons why this claim request could not have been filed earlier, namely in the proceedings before the opposition division.

9. Furthermore, the board could not identify in the decision under appeal any issues which the amendment in

question might be meant to address. Instead, in view of the changed wording, new issues not yet addressed in the proceedings before the opposition division would have had to be addressed for the first time at the appeal stage.

10. In view of the above considerations, the board decided to not admit the request into the proceedings under Article 12(4) RPBA 2007.

Auxiliary request 20A
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

11. Claim 1 of auxiliary request 20A is directed to "a pharmaceutical composition comprising" a polypeptide as defined in claim 1 of the main request.

12. This claim request was filed more than two years after the patent proprietor's reply to the opponents' appeals and represents an amendment to the patent proprietor's case. Its admittance into the appeal proceedings is governed by the provisions of Article 13(1) RPBA 2007 stipulating that any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at a board's discretion, which is exercised, *inter alia,* in view of the complexity of the new subject-matter, the current state of the proceedings and the need for procedural economy.

13. The case law of the boards of appeal has established criteria for when the late filing of requests could be in keeping with procedural economy, for example: the requests are an immediate reaction to unforeseeable developments in the previous proceedings; they are *prima facie* allowable; they are not unsuitable from the

outset to overcome doubts as to the allowability of the claims.

14. The patent proprietor submitted that the claim request included amendments to address objections under Article 123(2) EPC and constituted a reaction to the filing by opponent 2 of decision T 628/15 of this board in a different composition, allegedly dealing with closely related subject-matter.

15. However, a board of appeal is not bound by a board of appeal's decision in another case. Thus, irrespective of the similarity of wording between the claims and description in this appeal and the claims and description in the patent application underlying decision T 628/15, the filing of that decision by opponent 2 was not a development of the proceedings appropriate to trigger the filing of this claim request.

16. Moreover, the amendments were meant to address objections under Article 123(2) EPC put forward in respect of claim 1 of auxiliary request 21 already in opponent 1 and 3's statements of grounds of appeal (see point 5.1 and points 3.1 to 3.6, respectively) concerning the combination of VH and VL CDRs. *Prima facie*, it is not evident how inserting "pharmaceutical composition" into claim 1 can address these objections. Therefore, neither can the amendment in auxiliary request 20A be considered *prima facie* suited to overcome the objections; nor can it be considered an immediate reaction.

17. Moreover, at the oral proceedings, the patent proprietor submitted that claim 1 as amended had the format of a purpose-limited product claim according to

Article 54(4) EPC. This reading of claim 1 is not straightforward given that this provision refers to compositions "for use in a method referred to in Article 53(c) EPC", but in claim 1 the wording "pharmaceutical composition" is not followed by any medical purpose. Therefore, in view of this amendment, the set of claims, if admitted, would have entailed new considerations on claim construction not yet forming part of the proceedings and thus would have added to the complexity of the appeal case.

18. Finally, claim 1 further includes the wording "having" in the definition of the CDRs which, in the context of the main request, was objected to for lack of clarity. Also for this reason, the amendment introduced further complexity (see point 6. above).

19. Accordingly, the board, exercising its discretion pursuant to Article 13(1) RPBA 2007, decided not to admit auxiliary request 20A into the appeal proceedings.

Auxiliary requests 20B and 20C
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

20. Claim 1 of these requests includes the amendment carried out in auxiliary request 20A. Additionally, with respect to claim 1 of the main request and claim 1 of auxiliary request 20A, one of the two alternative CDR-H3s listed in the disclaimer has been deleted. Accordingly, the sets of claims of auxiliary requests 20B and 20C differ from each other in which of the alternative CDR-H3s has been deleted from the disclaimer in claim 1.

21. As concerns the amendment to "a pharmaceutical composition", the considerations above in the context of auxiliary request 20A also apply to these requests (see points 12., 16. and 17.).

22. As regards the amendment by which one of the alternative CDR-H3s was deleted, the patent proprietor submitted that it constituted a reaction to the objections raised by opponent 6 in the letter dated 11 July 2017, point 7.4. However, that letter constitutes that party's reply to the patent proprietor's appeal. It was thus filed at the first opportunity in the appeal proceedings. Filing auxiliary requests 20B and 20C in September 2019, i.e. more than two years after the objection was raised, cannot be considered an immediate reaction to these objections (see point 13. above).

23. Thus, the board decided not to admit auxiliary requests 20B and 20C into the appeal proceedings (Article 13(1) RPBA 2007).

Auxiliary request 20D
Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

24. Claims 1 and 2 of this claim request are identical to claims 3 and 4 of the main request.

25. The patent proprietor submitted that this claim request was filed in reaction to the filing by the opponents of decision T 628/15 in appeal proceedings and to the objection to added subject-matter in relation to auxiliary request 21. However, in the board's view, the considerations set out above in points 15. and 16., first sentence, still applied.

26. Moreover, as argued by the opponents, in light of this amendment, admittance of this set of claims would have increased the complexity of the proceedings because the current definition of the antibody by means of three CDRs only had not been considered in the opposition proceedings and accordingly was not addressed in the decision under appeal. This applies in spite of the fact that the same subject-matter was present in the form of claims 4 and 5 of the patent as granted.

27. Thus, the board decided not to admit auxiliary request 20D into the appeal proceedings (Article 13(1) RPBA 2007).

Auxiliary request 21 - claim 1

28. Auxiliary request 21 is identical to auxiliary request 18 held allowable by the opposition division in the decision under appeal. Claim 1 is directed to a bispecific polypeptide comprising a first and a second binding domain, the first binding domain being an antibody which binds to CD3ε of the species recited in the claim. In the following, it is this first binding domain which is considered when referring to an antibody.

29. The appellant-opponents contested the decision with regard to (i) allowability of the amendments under Article 123(2) EPC (except for claim 13), (ii) sufficiency of disclosure, (iii) inventive step and (iv) entitlement to priority.

Amendments (Article 123(2) EPC)

30. The opponents submitted that the subject-matter of claim 1 extended beyond the content of the application as filed in three respects: (i) the combination of CDRs of the variable light region with those of the variable heavy region; (ii) the combination of the three species recited in the claim with the specific epitope comprising the amino acid sequence Gln-Asp-Gly-Asn-Glu and (iii) the peptide itself which was not disclosed in the application as filed.

Admittance into the appeal proceedings of an objection under Article 123(2) EPC (Article 12(4) RPBA 2007)

31. Objection (i) above was put forward for the first time in appeal proceedings.

32. The claim request of current auxiliary request 21, then auxiliary request 18, had been filed two months before the oral proceedings before the opposition division. Hence, the parties had an opportunity to raise objections in the proceedings before the opposition division, at the latest at the oral proceedings. However, the decision under appeal states that the opponents had no objections under Article 123(2) EPC (point 10 of the Reasons, see also points 11.4 and 11.5 of the minutes of the oral proceedings before the opposition division).

33. Thus, the board concludes that the objection could and should have been put forward earlier and, exercising its discretion under Article 12(4) RPBA 2007, decided to not admit the objection into the appeal proceedings.

Further objection under Article 123(2) EPC

34. Objection (ii) above relates to the issue of whether the combination of (a) the three New World monkey species recited in the claim with (b) the specific peptide comprised in the epitope to which the polypeptides bound was disclosed in the application as filed. It was furthermore argued (iii) that the peptide itself was not disclosed in the application as filed.

35. Key for deciding on this matter is the interpretation of the passage of the application on page 26, lines 10 to 11 in the context of the application as a whole. This passage reads: "*More preferably, wherein said epitope comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu (Q-D-G-N-E-D).*"

36. The skilled person reading this passage is presented with a pentapeptide sequence in a three-letter code followed in brackets by a sequence in a one-letter code, which corresponds to the first peptide with one additional amino acid at the end, "D". The opponents argued, on the one hand, that it is not clear from this passage which of the two sequences is meant to represent the epitope and, on the other hand, that the passage discloses two alternatives, from which one was selected in claim 1.

37. Contrary to the opponents' arguments, the board is of the view that it is immediately apparent from this passage that the sequence in brackets - the second sequence - does not represent an alternative to the first sequence. Instead, the second sequence is merely intended to provide the one-letter code corresponding to the three-letter code Gln-Asp-Gly-Asn-Glu. This is apparent from the use of brackets. Additionally, the

reading of two alternatives, as proposed by the opponents, does not seem to be consistent with the use in the same sentence of a three-letter code in one instance and a one-letter in the other instance to represent two alternatives.

38. Furthermore, an issue of dispute was whether the peptide disclosed to the skilled person reading this passage in the context of the application as a whole was the three-letter code pentapeptide or the one-letter code hexapeptide.

The application discloses, on lines 1 to 6 preceding the above passage on page 26, that the epitope is part of an amino acid sequence consisting of 27 amino acids comprised in SEQ ID NOs 2, 4, 6 and 8. As argued by the patent proprietor, and not disputed by the opponents, those sequences comprise the pentapeptide in claim 1 but do not comprise the extra amino acid in the hexapeptide depicted in brackets on page 26 of the application. It can thus be concluded that the hexapeptide cannot represent the epitope included in SEQ ID NOs 2, 4, 6 and 8. This reading is also confirmed in the application on page 8, lines 23 to 30. This passage discloses the epitope in the form of the amino acids in CD3 epsilon which are critical for binding, listing the amino acids in positions 1 to 5 of the 27 amino acid fragment mentioned on page 26: Q, D, G, N and E. These amino acids correspond to the pentapeptide in claim 1.

39. In view of the above, the board cannot see any merit in the argument that a possible reading to solve the inconsistency between the two sequences on page 26 of the application would be to read that the epitope comprised the hexapeptide given in brackets, by which

the last amino acid, which is not present in SEQ ID NOs 2, 4, 6 and 8, would need to be corrected to read the amino acid "E".

40. It follows from the above conclusion that the combination objected to in claim 1 constitutes at most a combination of the peptide as disclosed in the application as filed, with a selection of the three species *Callithrix jacchus*, *Saguinus oedipus* and *Saimiri sciureus*. There is therefore no combination of two features each representing a selection.

41. Thus, the combination of features at issue does not lead to subject-matter extending beyond the content of the application as filed.

Sufficiency of disclosure (Article 83 EPC)

42. With the statement of grounds of appeal, opponent 1 contested the decision of the opposition division with respect to the requirement of sufficiency of disclosure (see statement of grounds of appeal, point 4.1.). This objection was maintained at the oral proceedings before the board without any oral submissions.

43. The patent proprietor requested that the objection not be admitted on the grounds of lack of substantiation.

44. The board considered the objection in the appeal proceedings under Article 12(4) RPBA 2007 but found the objection to be without merit on the substance (see below).

45. At issue was that the second binding domain of the polypeptide defined in claim 1 was not limited to an

antibody. However, the patent did not disclose "binding domains" other than antibodies.

46. The invention claimed lies in the characteristics of the first binding domain. Opponent 1 has neither provided arguments addressing the reasoning of the opposition division on this issue, which pointed to the lack of serious doubts substantiated by verifiable facts, nor evidence to the effect that the skilled person would not be in the position to provide "second binding domains" with the function required by the claim, namely "capable of binding to a cell surface antigen which is a tumour antigen".

47. Therefore, the objection of lack of sufficiency of disclosure does not succeed.

Inventive step (Article 56 EPC)

Introduction

48. After having considered which of the several documents referred to by the opponents did not qualify as closest prior-art documents, the opposition division held the claimed subject-matter to involve an inventive step in view of document D3 as representing the closest prior art.

The appellant-opponents contested this decision. Each of documents D6, D3, D11 and D50 was considered to represent the closest prior art. In the appeal proceedings, two further starting points for the assessment of inventive step were pursued: document D48 and the commercially available antibody SP34.

Admittance of the objection based on antibody SP34 as representing the closest prior art (Article 13(1) RPBA 2007)

49. With opponent 4's letter of 17 March 2021, an objection of lack of inventive step was developed starting from the commercially available antibody SP34 as the closest prior art.

50. It has not been submitted by opponent 4 that this objection had already been filed at an earlier point in time. Thus, the submission of this objection is an amendment of the case.

51. One of the criteria stipulated in Article 13(1) RPBA 2007 for deciding if an amendment to a party's case may be admitted is the need for procedural economy (see point 13. above).

52. In relation to late-filed facts and evidence, it is established case law of the boards of appeal that, considering that the boards have to ensure that proceedings are conducted expeditiously and that parties are fairly treated, the parties should submit all the facts evidence and arguments relevant to their case as early and completely as possible, in particular when such evidence was already known to the party concerned.

53. No reasoning was provided in favour of the admittance of this objection into the appeal proceedings.

54. The claim set of current auxiliary request 21 is that of then auxiliary request 18 filed two months before the oral proceedings in opposition and found allowable by the opposition division. The board therefore came to the conclusion that the objection at issue has not been

submitted as early as possible. Furthermore, the commercially available antibody had been known to opponent 4 as it had previously been addressed in the context of novelty.

55. Therefore, the board decided not to admit the objection into the appeal proceedings (Article 13(1) RPBA 2007).

Admittance of the objection based on document D48 as representing the closest prior art (Article 13(1) RPBA 2007)

56. At the oral proceedings, opponent 4 also relied on document D48 as the starting point for the assessment of inventive step.

57. Opponent 4 submitted that a line of argument starting from document D48 as the closest prior art had been presented before in the appeal proceedings with opponent 1's reply to the patent proprietor's statement of grounds of appeal. Opponent 4 pointed to the following passages: points 3.16, 3.60, 7.10 and 7.39.

58. Point 3.16 of that letter develops arguments under the heading "*Lack of novelty over D48*". It provides a summary of the disclosure in document D48 and concludes that the subject-matter of claims 15 to 18 and 19 to 21 of the then main request lacks novelty.

Point 3.60 also concerns the then main request stating that the "*claims also lack inventive step, over at least D11 and D48*".

Point 7.10 provides arguments under Article 123(2) EPC relating to then auxiliary requests 16 to 20. The only mention of document D48 is in the context of the disclaimer in claim 1 of those requests as follows:

"*D48 is in the same field as the patent (it relates to CD3-binding antibody-based molecules) and therefore cannot be considered an accidental anticipation.*"

Point 7.39 relates to then auxiliary request 20, now the main request, and concerns lack of novelty of the subject-matter of claim 1 in view of document D6. It refers to a "*potential lack of novelty over D48*".

59. As apparent from the above, of the four passages pointed to by opponent 4, only point 3.60 mentions document D48 in the context of inventive step. However, in the above-quoted passage, the board cannot find any reasoning why the subject-matter of the claims of the then main request would not involve an inventive step, let alone find any reasoning that would apply to auxiliary request 21 before the board. Therefore, no inventive-step objection based on document D48 as representing the closest prior art has been substantiated prior to the oral proceedings before the board.

60. The board therefore came to the conclusion (see also point 54. above) that the objection at issue has not been submitted as early as possible in a substantiated manner. Furthermore, document D48 had been known to opponent 4 before the oral proceedings as it had previously been addressed in the context of novelty.

61. In view of the above considerations, the board decided not to admit the objection into the appeal proceedings (Article 13(1) RPBA 2007).

Inventive step in view of document D6 as representing the closest prior art

62. In one of the inventive-step objections, document D6 was taken to represent the closest prior art to the claimed subject-matter. Its publication date lies between the dates of filing of the patent applications P2 and P3 from which priority is claimed. Therefore, the validity of the claimed priority was relevant.

Priority (Article 87 EPC)

63. It was common ground that the patent applications P1 and P2 disclosed the epitope sequence in claim 1 of auxiliary request 21.

64. The opponents submitted that patent applications P1 and P2 do not disclose the same invention as the one to which claim 1 is directed for two reasons.

65. It was submitted by the opponents that the effect of binding to the epitope on the reduction of T cell redistribution, as disclosed in the patent, resulted in a definition of the epitope different to that disclosed in the priority applications P1 and P2, where this effect was not disclosed. In other words, the definition of the epitope was not the same as disclosed in the priority applications P1 and P2. Whereas the epitope disclosed in the priority applications was only structurally defined, in the patent it was defined additionally in functional terms, and hence the invention claimed was not the same as that disclosed in priority applications P1 and P2.

66. Claim 1 does not include the functional feature "reduced T cell redistribution".

67. The epitope is structurally defined in claim 1, as follows: "the epitope is part of an amino acid sequence comprised in the group consisting of SEQ ID NOs:2, 4, 6, or 8 and comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu." There is no lack of clarity in this definition.

68. In accordance with the case law of the boards of appeal, if a term used in a claim has a clear technical meaning, the description cannot be used to interpret that term in a different way (see also decisions T 2221/10, T 197/10 and further decisions cited in Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, II.A.6.3.4, second paragraph and following).

69. The board concludes that the subject-matter claimed does not involve a definition of the epitope different to the structural definition by means of the amino acid sequence recited in the claim. Accordingly, the board sees no merit in the opponents' objection.

70. Furthermore, the opponents submitted that the priority applications P1 and P2 only disclosed binding domains derived from humans.

71. The passages referred to by opponent 7 do indeed disclose human binding domains. However, the priority applications P1 and P2 also disclose non-human binding domains, such as mouse and humanised binding domains (see example 2.6). Therefore, the opponent's argument is not convincing.

Inventive step in view of document D3, document D11 or document D50 as representing the closest prior art

72. The parties considered the disclosure in each of documents D3, D11 and D50 to represent equivalent starting points for the assessment of inventive step. Indeed, it was not argued that the relevant subject-matter disclosed in these documents differed.

In the following, document D11 is analysed.

73. Document D11 discloses bispecific antibodies for use in cancer treatment. Various formats are described, including scFv, and characteristics of these constructs relevant for clinical application are discussed. Various constructs targeting CD3 are disclosed, but no specific sequences of their respective variable domains are (see Abstract, Figure 1 and Table 1).

74. As submitted by the opponents, the following differences between the subject-matter of claim 1 and this prior art exist: the CD3 epitope to which the bispecific polypeptide binds and the specific sequences of its CDRs.

75. The parties were in dispute as to the technical effects that may be attributed to these differences. The patent proprietor and the opponents were in agreement that a technical effect that could be attributed to the different epitope was the ability of the polypeptide to cross-react with human and the New World monkey species recited in the claim. However, the opponents contested the presence of an effect in terms of reduced T cell redistribution, as submitted by the patent proprietor.

76. The opponents moreover argued that the cross-species reactivity was not demonstrated for all embodiments claimed. The board is not persuaded by this argument.

Indeed, the epitope is a feature of the claim. The binding to an epitope available on the CD3 of the species recited in the claim results in the technical effect of cross-species binding, irrespective of the CDRs. Moreover, the cross-species reactivity is also a feature of the claim since its wording requires that the CD3 binding domain is "capable of binding to an epitope of human and Callithrix jacchus, Saguinus oedipus or Saimiri sciureus CD3ε chain, wherein the epitope ... comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu".

There is experimental evidence in document D112 showing, for ten different polypeptides falling within the claim, binding to the epitope. There is no evidence of a polypeptide encompassed by the claim not binding to the epitope.

77. In light of the technical effect which is not disputed by the parties and which in the board's view can be acknowledged (see point 76.), the objective technical problem is to be formulated as the provision of a bispecific CD3 and tumour binding polypeptide which binds to human and New World monkey CD3.

78. This formulation of the objective technical problem does not take into account the second technical effect alleged by the patent proprietor, namely increased efficacy due to reduced T cell redistribution. However, in view of the opponents' submissions that no such technical effect can be acknowledged and further in view of the board's conclusion that the claimed

subject-matter involves an inventive step taking into account the first technical effect only, no reasons need to be given in this respect.

79. The skilled person faced with the problem set out in point 77. would not have provided a bispecific polypeptide in which the CDR3 binding domain had the CDRs and displayed binding to the epitope as defined in the claim.

80. It was disputed by the parties whether the skilled person would have provided a solution based on the commercially available antibody SP34. According to the experimental evidence submitted by the appellant-opponents, this antibody binds to the epitope defined in the claim (see documents D18a, D19, D52a and D101).

81. The skilled person was aware of antibodies binding to CD3 as disclosed in document D39. However, the only commercially available antibody showing binding to New World monkey CD3 was antibody SP34. The board thus concurs with the opponents that the skilled person faced with the above formulated objective technical problem would have used SP34 as a building block in the development of the bispecific polypeptide.

82. The patent proprietor contested this view. However, the reasons of the board on this issue do not need to be outlined because of the conclusion below.

83. It was common ground that the CDR sequences of the CD3 binding domain in claim 1 differed from those of antibody SP34. Thus, the solution arrived at by the skilled person, when modifying the closest prior-art antibodies by using the CD3 binding domains of this antibody, would not be encompassed by the claim.

84. In view of the fact that the CDRs of the SP34 antibody determined its binding to CD3 of New World monkeys and provided the skilled person with a solution to the posed problem, the board has not seen any persuasive argument why the skilled person would have provided, as CD3 binding domains, variants of the SP34 antibody by modifying its CDR sequences. The opponents' argument that the CDRs of antibody SP34 could be routinely modified by mutagenesis is therefore not relevant.

85. Furthermore, under the assumption that the skilled person would have been motivated to provide a polypeptide based on variants of antibody SP34, the board is not convinced that such variants would be encompassed by claim 1 as submitted by the opponents.

86. The opponents submitted that the skilled person would have generated such variants by mutagenesis of the CDRs and testing for cross-reactivity. In the board's view, the suggested mutation of the CDRs of antibody SP34 and selection for cross-reactivity might have resulted in alternative cross-reacting CD3 binding domains but would not necessarily have resulted in domains that bind to the same epitope as SP34. Since the claim is directed to only those constructs that bind to the same epitope, which had not yet been identified, this would not have led to a bispecific construct falling within the scope of the claim.

87. In view of point 72., the same considerations apply when starting from documents D3 and D50 as representing the closest prior art.

88. Consequently, the opponents' objection of lack of inventive step against claim 1 of auxiliary request 21 does not succeed.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated