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Datasheet for the decision of 14 September 2023

Case Number: T 0885/21 - 3.3.07

Application Number: 13786322.1

Publication Number: 2911699

IPC: A61K47/68

Language of the proceedings: EN

Title of invention:
MODIFIED ANTIBODY, ANTIBODY-CONJUGATE AND PROCESS FOR THE PREPARATION THEREOF

Patent Proprietor:
Synaffix B.V.

Opponents:
HGF Limited
Glykos Finland Oy
Genovis Ab

Headword:
Modified antibody / SYNAFFIX

Relevant legal provisions:
RPBA 2020 Art. 12(4)
EPC Art. 114(2), 84, 123(2), 83, 54(2), 54(4), 56

Keyword:

Amendment to case - main request admitted (yes)
Late submitted objections - admitted (no)
Claims - clarity (yes)
Amendments - added subject-matter (no)
Sufficiency of disclosure (yes) - serious doubts (no)
Novelty - availability to the public (yes) - implicit disclosure medical use (no)
Inventive step - relevance post-published evidence (yes) - unexpected improvement (yes)

Decisions cited:

G 0004/19, G 0002/21

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Case Number: T 0885/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 September 2023

Appellant: (Patent Proprietor)	Synaffix B.V. Kloosterstraat 9 5349 AB Oss (NL)
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Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 21 April 2021 revoking European patent No. 2911699 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Usuelli
Members: M. Steendijk
A. Jimenez

Summary of Facts and Submissions

I. European patent 2 911 699 ("the patent") was granted on the basis of fourteen claims.

The patent as granted related *inter alia* to methods for preparing conjugates from a modified antibody comprising a N-acetylglucosamine ("GlcNAc") linked sugar derivative ("S") having an azido group with a linker-conjugate comprising a cycloalkynyl group and a molecule of interest (claims 1-5), conjugates obtainable with such methods defined by a structural formula (claims 6-8) or defined as a product-by-process (claim 9) and such conjugates for use in therapy (claim 10), in particular in treatment of cancer (claim 11).

II. Three oppositions had been filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

The decision was based on

- the main request relating to the patent as granted,

- auxiliary request 1 filed as request Ia on 10 December 2020,

- auxiliary requests 2-4 filed during the oral proceedings held on 11 February 2021,

- auxiliary requests 5-13 filed as auxiliary requests I-IX on 10 December 2020,

- auxiliary requests II"a" - V"a" filed on 10 December 2020.

In its decision the opposition division cited *inter alia* the following documents:

D12: WO 2008/029281 A2
D13: WO 2007/095506 A1
D17: Accounts of Chemical Research, 2011, 44(9), 805-815
D20: Adv. Drug Deliv. Rev., 2008, 60(12), 1407-1420
D22: "Cycloalkyne", Wikipedia, obtained 27 July 2018 from https://en.wikipedia.org/wiki/Cycloalkyne
D23: Aggeler et al., 2011: "Site-specific click chemistry-mediated labeling of antibody glycans using metabolic and enzymatic approaches. Poster published at The Essential Protein Engineering Summit, 9-13 May 2011, Boston, MA, USA
D23b: Declaration by Dr Agnew signed on 9 August 2018
D23c: Declaration by Dr Agnew signed on 16 July 2019 with Annexes A to E
D41: WO 2007/133855 A2
D51: Declaration by Dr. Floris Louis van Delft - Glycan based conjugation technologies for the medical application of antibody conjuqates
D52: Bioconjugate Chem., 2002, 13, 47-58
D66: Anqew. Chem. Int. Ed., 2010, 49, 9995-9997
D70: Nature Biotechnology, 2008, 26(8), 925-932
D71: PNAS, 2012, 109(40), 16101-16106
D72: Nature Biotechnology, 2012, 30(2), 184-189
D73: Discovery Medicine, 2010, 10(53), 329-339
D85: Toxins, 2011, 3, 848-883

The opposition division arrived at the following conclusions:

(a) The subject-matter of dependent claim 4 as granted was not sufficiently disclosed, because it defined a method which specifically included the use of cycloalkynes with less than 8 ring members, whereas it was not credible that the method could be carried out with cycloalkynes with less then 8 ring members.

Moreover, the therapeutic utility defined in claims 10 and 11 as granted was not sufficiently disclosed, because it was not plausible that all antibodies and all conjugated "molecules of interest" would be suitable for use in therapy, let alone in treatment of cancer.

(b) Auxiliary requests 1 and 2 did not comply with Rule 80 EPC.

(c) In auxiliary request 3 the "molecule of interest" was limited to a cytotoxin, the antibody was defined to specifically bind cancer antigen, the GlcNac was qualifed as "core N-acetylglucosamine" and the explicit definition of a cycloalkyne with less then 8 ring members was eliminated.

This request complied with Rule 80 and Articles 84, 123(2) and 83 EPC.

The claimed subject-matter was not disclosed in document D23, because it was not evident that the agent "Qdot 625" described in document D23 represented a cytotoxin.

The most restrictive claim 10 of auxiliary request 3 defined the conjugates comprising the anti-cancer antibody with the cytotoxin for use in the treatment of cancer. With respect to this subject-matter document D13 represented the closest prior art. The difference between the claimed subject-matter and the teaching in document D13 concerned the selection of an anti-cancer antibody to be trimmed to the core N-acetylglucosamine together with a cytotoxin to be used in the treatment of cancer as well as use of a linker with a (hetero)cycloalkynyl group. The problem to be solved was the identification of suitable antibodies for the treatment of cancer and a suitable coupling agent. The selection of the suitable antibodies was obvious in view of common general knowledge as reflected in documents D85 and D66. The use of cyclooctynes as coupling agents was already suggested by document D13 as well as document D17, which also mentioned lower toxicity from cyclooctynes with respect to copper requiring reagents. Accordingly, the subject-matter of auxiliary request 3 did not involve an inventive step.

(d) Auxiliary request 4 did not involve an inventive step for the same reason as auxiliary request 3.

(e) Auxiliary requests II"a"-V"a" did not comply with Rule 80 for the same reasons as auxiliary request 1.

(f) Auxiliary requests 5-13 comprised claims directed to the therapeutic utility of a conjugate in which the antibody is not limited to an antibody that binds a cancer antigen. Accordingly, auxiliary

requests 5-13 did not comply with Article 83 EPC for same reason as the main request.

III. With the statement of grounds of appeal the patent proprietor upheld the request for the patent to be maintained as granted (main request) and filed auxiliary requests 1 to 15.

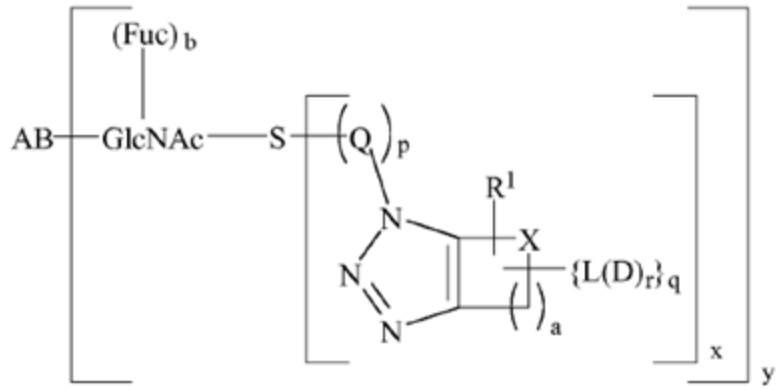
IV. The Board invited the parties to attend oral proceedings with the summons of 23 September 2022. In its communication pursuant to Article 15(1) RPBA of 2 February 2023 the Board expressed *inter alia* the preliminary opinion that auxiliary request 1 as filed with the statement of grounds of appeal met the requirements of the EPC.

V. With the letter of 14 July 2023 opponent 1 expressly presented an objection of lack of inventive step against auxiliary request 1 on the basis of document D23 as starting point in the prior art.

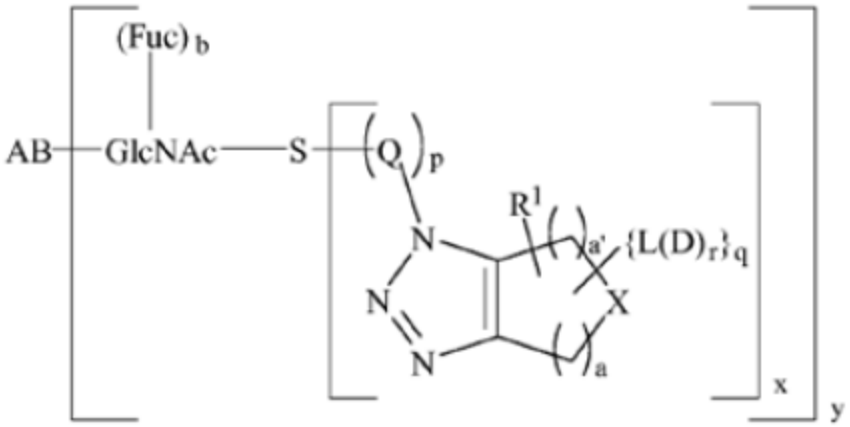
VI. With the letter of 31 July 2023 the patent proprietor withdrew the request regarding the patent as granted. Auxiliary request 1 as filed with the statement of grounds of appeal was renamed as the new main request.

Independent claim 1 of this new main request defines:

"Antibody-conjugate according to the Formula (20) or (20b) for use as a medicament:



20



20b

wherein:
L is a linker;
D is a cytotoxin;
r is 1 - 20;
R1 is independently selected from the group consisting of hydrogen, halogen, -OR5 , -NO2 , -CN, -S(O)2 R5 , C1 - C24 alkyl groups, C6 - C24(hetero)aryl groups, C7 - C24 alkyl(hetero)aryl groups and C7 - C24 (hetero)arylalkyl groups and wherein the alkyl groups, (hetero)aryl groups, alkyl(hetero)aryl groups and (hetero)arylalkyl groups are optionally substituted, wherein two substituents R1 may be linked together to

form an annelated cycloalkyl or an annelated (hetero)arene substituent, and
wherein R5 is independently selected from the group consisting of hydrogen, halogen, C1 - C24 alkyl groups, C6 -C24 (hetero)aryl groups, C7 - C24 alkyl(hetero)aryl groups and C7 - C24 (hetero)arylalkyl groups;
X is C(R1)2 , O, S or NR2 , wherein R2 is R1 or L(D)r , and wherein L, D and r are as defined above;
q is 0 or 1, with the proviso that if q is 0 then X is N-L(D)r ;
b is 0 or 1;
p is 0 or 1;
Q is -N(H)C(O)CH2 - or -CH2 -;
x is 1, 2, 3 or 4;
y is 1 - 20;
wherein in Formula (20) a = 5, 6 or 7,
wherein in Formula (20b)
a is 0, 1, 2, 3, 4, 5, 6 or 7;
a' is 0, 1, 2, 3, 4, 5, 6, or 7 and
a+a' is 5, 6, or 7,
and wherein AB is an antibody, wherein the antibody specifically binds cancer antigen,
S is a sugar or a sugar derivative,
GlcNAc is N-acetylglucosamine and Fuc is fucose and wherein GlcNAc is bonded via C1 to the AB via an N-glycosidic bond to the amide nitrogen atom in the side chain of an asparagine amino acid of the AB."

Independent claim 3 of the new main request defines:

"Antibody-conjugate for use as a medicament, wherein the antibodyconjugate is obtainable by a process comprising reacting a modified antibody with a linker-conjugate, wherein said linker-conjugate comprises a (hetero)cycloalkynyl group and one or more molecules of

interest, wherein said molecule of interest is a cytotoxin,
wherein said modified antibody is an antibody comprising a GlcNAc-S(A)x substituent, wherein GlcNAc is a core N-acetylglucosamine, wherein S(A)x is a sugar derivative comprising x functional groups A wherein A is an azido group and x is 1, 2, 3 or 4,
wherein said GlcNAc-S(A)x substituent is bonded to the antibody via C1 of the core N-acetylglucosamine of said GlcNAc-S(A)x substituent via a N-glycosidic bond to the amide nitrogen atom in the side chain of an asparagine amino acid of the antibody and wherein said GlcNAc is optionally fucosylated,
and wherein the antibody specifically binds cancer antigen."

VII. Oral proceedings were held on 14 September 2023. The oral proceedings were attended by the patent proprietor and opponent 1.

VIII. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

The main request was to be admitted into the appeal proceedings, because it did not give rise to any new issues with respect to auxiliary request 3 on which the decision under appeal was based. The objection against the admittance of the main request due to impermissible double patenting as raised by opponent 1 during the oral proceedings was not to be admitted, because it was late filed and lacked *prima facie* relevance.

The conclusions in the decision under appeal regarding the requirements of Articles 84, 123(2) and 83 EPC with respect to what was then auxiliary request 3 applied to the main request.

It had not been demonstrated that document D23 was part of the prior art. Document D23 did anyway not disclose any therapeutic utility of the described antibody conjugates and the disclosed conjugates would in fact not be suitable for therapeutic use.

The objection of lack of inventive step starting from document D23 was not to be admitted, because it was filed at a late stage of the appeal proceedings and *prima facie* lacked relevance.

The patent demonstrated with experimental results the therapeutic utility of the conjugates of the main request. Document D52 represented the closest prior art, because it actually related to conjugates of an antibody with a glycan linked cytotoxin for use in therapy. The difference of the claimed subject-matter with the teaching of document D52 concerned the conjugation by click-reaction to a sugar moiety linked to the core GlcNAc of the antibody instead of conjugation by reaction of a hydrazone to an oxidized glycan moiety of the antibody. Document D13 mentioned the possible conjugation of a cytotoxin to an antibody, but only within the context of a variety of strategies for modifying antibodies and without disclosure of any suitable starting point in the form of an example of a cytotoxin-antibody-conjugate for use in therapy.

Document D51 demonstrated the optimized properties of the claimed conjugates in terms of homogeneity, reduced Fc-gamma binding, reduced susceptibility to elastase cleavage, pharmacokinetic profile and *in vivo* efficacy in comparison to conjugates in which the cytotoxin is linked by reaction of a hydrazone to an oxidized glycan or linked to a distal terminal GlcNAc group. The prior

art provided no suggestion towards the claimed subject-matter as solution to the problem of providing conjugates with such improved properties.

IX. The arguments of the opponents relevant to the present decision are summarized as follows:

The main request was not to be admitted, because it was only filed for the first time with the statement of grounds of appeal without justification and without indication of the basis of the amendment in the application as filed, because it did not address a ground of opposition and because it was part of a non-convergent set of auxiliary requests. Moreover, the main request should not be admitted to prevent impermissible double patenting, since it defined subject-matter that had essentially already been defined in a patent from a divisional application granted to the proprietor on 12 April 2023.

The expressions "cytotoxin" and "wherein the antibody specifically binds cancer antigen" as introduced in the claims of the main request lacked clarity.

The main request related to subject-matter extending beyond the content of the application as originally filed due to the combination of the specified values for "a" and "a'" in claims 1 and 6 and the definition of the "core-GlcNAc" in claim 3 with the limitations to a cytotoxin and an antibody specifically binding cancer antigen.

Claim 1 of the main request defined compounds in which "a" or "a+a'" are 6 or 7, which required for their preparation the conjugation of a compound carrying a 9 or 10-membered (hetero)cycloalkynyl group. Claim 3 of

the main request referred generically to conjugation with a "(hetero)cycloalkyl group". The patent did not sufficiently the disclose how to prepare the defined compounds within the whole scope of these definitions. Moreover, due to the generic definition of the cytotoxic agent, the antibody and the linker the definition of the conjugates comprised compounds which were not suitable for the defined therapeutic use. The patent did therefore not sufficiently disclose the claimed utility within the whole scope of the claims.

Claim 1 of the main request lacked novelty in view of document D23. Document D23 represented prior art explicitly disclosing a conjugate as claimed and implicitly disclosing its use in therapy.

The subject-matter of the main request lacked an inventive step in view of any of documents D52, D13, D12 or D23 as starting point in the prior art. The objection starting from document D23 had been indicated by opponent 1 in its reply to the statement of grounds by reference to an annexed submission filed during proceedings before the opposition division.

Post-published evidence relied upon by the proprietor should not be taken into account. No particular effect had anyway been demonstrated in post-published document D52 for the whole scope of the claims taking account of the generic structural definitions in the claims. Moreover, no comparative results with the closest structures disclosed in documents D13 and D23 had been presented.

Starting from document D52 it was anyway obvious to provide an antibody conjugate as defined in accordance with the main request in view of documents D23 or D13,

which indicated advantageous properties for conjugates from antibodies trimmed to the core-GlcNAc as defined in the main request.

Starting from document D13 the skilled person would regard the conjugates from trimmed antibodies defined according to the main request obviously suitable for use in treatment of cancer, because documents D12, D13, D23 and D41 already described the preparation of conjugates with trimmed antibodies, whilst document D13 explicitly referred to the use of cancer specific antibodies and conjugates with a cytotoxin. Moreover, document D13 itself as well as document D23 pointed at the advantages of the site-specific conjugation via click reaction to a modified glycan moiety. Any demonstrated advantage would further be obvious in view of documents D66 and D70-D73.

Starting from document D23 the skilled person would consider the therapeutic utility of the claimed conjugates of cytotoxins with cancer binding antibodies linked via the core GlcNAc group obvious on the basis of the common knowledge as represented by document D20 as well as in view of documents D13 or D52.

X. The patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or auxiliary requests 1-14, which had been filed as auxiliary requests 1-15 with the statement of grounds of appeal.

XI. The opponents requested that the appeal be dismissed and the patent be revoked in its entirety.

The opponents further requested that the new main request and auxiliary requests 1-14 not be admitted.

Reasons for the Decision

1. Admittance of the new main request

1.1 The claims of the new main request are limited to a conjugate of an anti-cancer antibody with a cytotoxin for use as a medicament. The main request is thereby in substance restricted to the subject-matter of claims 9 and 10 of auxiliary request 3 as filed before the opposition division, which was found to lack an inventive step in the decision under appeal. The request does not raise new issues and addresses the finding on sufficiency in the decision under appeal regarding the claims as granted. As the decision under appeal denied that the mentioned claim 10 of auxiliary request 3 involved an inventive step, it served no purpose for the proprietor to file the new main request during the first instance proceedings.

1.2 The mere circumstance that lower ranking auxiliary requests comprise claims for subject-matter extending beyond the scope of the claims of the main request does not affect the admittance of the higher ranked main request.

1.3 The Board has not admitted the objection against the main request for impermissible double patenting following the grant of a patent from a divisional application, because this objection was late filed and lacked *prima facie* relevance (Article 114(2) EPC).

Opponent 1 raised this objection for the first time as late as during the oral proceedings of 14 September 2023, although opponent 1 reported that the patent from the divisional application had been

granted on 12 April 2023. In the Board's view the lateness of the objection is not excused by the statement that opponent 1 only became aware of the grant from the divisional application two days before the oral proceedings. The Board further observes that the prohibition of double patenting as recognized in G 4/19 does not represent a ground of opposition and that it is not at all evident that opposition and appeal proceedings relating to an earlier granted patent should be affected by the subsequent grant from a divisional application.

1.4 The Board has therefore admitted the main request into the appeal proceedings (Article 12(4) RPBA).

2. Clarity

In its communication pursuant to Article 15(1) RPBA (see section 8) the Board expressed *inter alia* the preliminary opinion that it agreed with the finding in the decision under appeal (see section 9.3) that the introduced expressions "cytotoxin" and "wherein the antibody specifically binds cancer antigen" are clear to the skilled person who works in the field of antibodies for use against cancer. As no substantive arguments were submitted by the opponents in response to the Board's preliminary opinion regarding the clarity of said expressions the Board confirms its opinion that the main request is not objectionable for lack of clarity.

3. Article 123(2) EPC

The patent application as originally filed (see WO2014/065661) describes on page 61, lines 25-26, and page 70, lines 8-15, that the conjugates for use as a

medicament preferably comprise an antibody that specifically binds cancer antigen and a molecule of interest which is a cytotoxin. The original application further clearly describes that "a" and "a+a'" may have the values of 5, 6 or 7 (see page 58) and that the N-acetylglucosamine substituent to the antibody is a core-GlcNAc substituent (see page 19).

In its communication pursuant to Article 15(1) RPBA (see section 8) the Board expressed its preliminary opinion that in line with the findings in the decision under appeal regarding the then auxiliary request 3 (see section 8) the subject-matter defined in the new main request met the requirement of Article 123(2) EPC. As no substantive arguments were submitted by the opponents in response to the Board's preliminary opinion regarding the compliance of the main request with Article 123(2) EPC the Board confirms its opinion that the main request meets the requirement of Article 123(2) EPC.

4. Sufficiency

4.1 The claims of the main request define conjugates of an antibody specifically binding cancer antigen with a cytotoxin for use as a medicament. The cytotoxin is conjugated via a sugar derivative S attached to the core GlcNAc of the antibody. In claim 1 the link between the sugar derivative and the cytotoxin includes a condensed triazole, which may in line with the process described in the patent (see e.g. paragraphs [0227]-[0231]) be obtainable by click reaction of an azide group linked to the sugar derivative with a cycloalkynyl group linked to the cytotoxin. In claim 3 the conjugate is explicitly defined as obtainable from

reaction of an azide on the sugar derivative with a cycloalkynyl group linked to the cytotoxin.

4.2 In accordance with the established jurisprudence (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, III.G.5.c) a successful objection of insufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts, for which in case of *inter partes* proceedings the burden of proof initially lies with the opponent, who must establish, on the balance of probabilities, that a skilled person reading the patent, using common general knowledge, would be unable to carry out the invention.

4.3 In the present case the opponents objected that the claims of the main request would be bound to cover conjugates unsuitable for use as a medicament in view of the broad definitions of the cytotoxin, the antibody and the linker. This would for instance be evident from the numerous antibody-cytotoxin conjugates that had failed in clinical trials due to toxicity or lack of efficacy and from common general knowledge as represented by document D85, which indicates the criticality of the linkage between antibody and the cytotoxin (see D85, abstract). The invention could therefore not be carried out within the whole scope of the claims. The patent would thus leave the skilled person with the undue burden of selecting suitable cytotoxins, antibodies and linkers. This undue burden was illustrated by the proprietor's argument that conjugates as described in document D23 would not be suitable for use as a medicament.

The opponents further maintained that in view of the commonly known lack of stability of cycloalkynes with less than 8 ring members and the reduced reactivity of

cycloalkynes with more than 8 ring members (see documents D17 and D22) the patent did not sufficiently disclose how to obtain the conjugates covered by claims 1 or 3 of the main request which required the reaction of cycloalkynes having more or less than 8 ring members.

4.4 The Board observes in the first place that the claimed invention relates to compositions for use as a medicament and thereby functionally excludes conjugates which are unsuitable for use in therapy. The Board further notes that the patent describes in its experimental section (see paragraphs [0260]-[0354] and Figures 22 and 24-30) the preparation of a variety of examples of conjugates from click reaction involving the sugar derivative GalNAz with a cyclooctyne linked cytotoxin as defined in the claims of the main request as well experimental results of in vitro and in vivo tests involving such conjugates which indicate *inter alia* efficacy in reducing tumor volume in a mouse xenograft model. The patent also presents lists of examples of suitable cytotoxins (see paragraphs [0137] and [0252]), suitable antibodies specifically binding cancer antigen (see paragraph [0253]) and suitable linker units (see paragraphs [0174]-[0179]). Without evidence to the contrary the Board considers that this information in the patent provides the skilled person with sufficient guidance to carry out the claimed invention.

The references by the opponents to conjugates which had failed in clinical trials due to toxicity or lack of efficacy have not been shown to actually involve conjugates covered by the main request. The common general knowledge in document D85 regarding the criticality of the linkage does not disqualify any

particular type of linker described in the patent. Such common general knowledge may actually be relied upon by the skilled person when selecting a suitable linker and does not reveal any lack of disclosure of the claimed invention in the patent. In this context the Board does not consider that the proprietor's assertion regarding the unsuitability of conjugates described in document D23 for use as a medicament represents evidence of any lack of sufficient disclosure of the claimed invention.

Documents D17 and D22 indeed indicate reduced strain and by consequence reduced reactivity of cycloalkynes with more than 8 ring members, but do not exclude the suitability of such larger cycloakynes to provide conjugates as covered by the claims by a click reaction (see D17, page 805, last paragraph and page 809 right column, under "Cyclooctyne"; see D22, under "Cycloalkyne" and under "Reactions"). The Board further considers that the common knowledge regarding the lack of stability of cycloalkynes with less than 8 ring members will actually assist the skilled person to select cycloalkynes suitable to provide the conjugates as defined in claim 3 of the main request.

Taking account of the established jurisprudence mentioned in section 4.2 above the Board therefore considers that the patent sufficiently discloses the subject-matter as defined in accordance with the main request.

5. Novelty

5.1 Public availability document D23

Document D23 relates to a poster, which according to declarations by one of its authors, Mr Agnew, had been

presented to the public during the 7th annual PEGS conference held on 9-13 May 2011, *i.e.* before the priority date claimed for the patent.

Mr Agnew has declared (see D23b) that he had personally hung the poster at the Exhibit Hall on 12 May 2011, where the poster could be inspected by the public, for instance during the poster presentation on 13 May 2011 between 7:45 and 8:30. Mr Agnew has further provided circumstantial evidence regarding the public presentation of the poster at the PEGS conference in 2011 (see document D23c) in the form of e-mail correspondence of Mr Agnew with the poster coordinator, Mr Ring, confirming the distribution of the poster abstract to the attendees (Annex A), the published poster abstract itself (Annex B), the Program Guide for the conference announcing poster presentations on 12 and 13 May with reference to the title of the poster of document D23 (Annex C), e-mail correspondence from 27 June 2011 of Mr Agnew with an attendee at the presentation regarding the subject of the poster (Annex D) as well as a screen shot presenting the pdf-meta-data for the poster of document D23, including its creation and modification on "2/4/2011" (Annex E).

The Board observes that the declarations by Mr Agnew are unequivocal and are corroborated by the presented circumstantial evidence.

The proprietor has argued that the circumstantial evidence in annexes A-E of document D23c does not allow to conclude with the required certainty that the full content of document D23 was publicly presented at the PEGS conference in 2011. The Board observes, however, that the annexes A-E are not relied upon as evidence of the publication of document D23 *per se*, but rather to

corroborate the declarations in documents D23b and D23c. Meanwhile the proprietor has provided no grounds to doubt the correctness of the declaration by Mr Agnew regarding the public display of the poster of document D23 at the PEGS conference in document D23b.

The Board therefore considers the unequivocal declaration by Mr Agnew regarding the public display of the poster of document D23 at the PEGS conference in document D23b together with the corroborating evidence regarding this public display presented with his declaration in document D23c convincing evidence that the poster of document D23 represents prior art under Article 54(2) EPC with respect to the subject-matter of the main request.

5.2 Novelty in view of document D23

The claims of the main request define conjugates for use as a medicament and are thus covered by the provision of Article 54(4) EPC concerning the novelty of compositions for use in a surgical, therapeutic or diagnostic method as referred to in Article 53(c) EPC.

Document D23 describes the enzymatic labeling of antibodies involving treatment with Endo F2 followed by transfer of GalNAz with GalT and conjugation with a DIBO-dye or DIBO biotin reporter label (see D23 "Materials and Methods"). Document D23 specifically reports the labelling of a pAKT antibody involving Endo F2 treatment leaving the GlcNAc residue bound to the antibodies asparagine residue with subsequent enzymatic GalNAz-transfer and biotin alkyne linking by click chemistry followed by conjugation with the fluorescent label SA-Qdot 625. Document D23 further reports *in vitro* results indicating that the click labeling of the

antibodies does not affect their binding activity (see D23, Figure 3).

Document D23 does not explicitly describe any use of the mentioned conjugates in a method as referred to in Article 53(c) EPC. Moreover, document D23 does not describe any experimental results involving the mentioned conjugates that would in any way necessarily imply a disclosure of their utility in a therapeutic, surgical or diagnostic method. On the contrary, document D23 explicitly includes the disclaimer: "For research use only. Not intended for any animal or human therapeutic or diagnostic use" (see document D23, right column, following "References").

The Board therefore concludes that document D23 does not deprive the subject-matter of the main request of novelty.

6. Inventive step

6.1 Description of the claimed invention in the patent

The subject-matter of the main request relates to antibody-cytotoxin conjugates for therapeutic use, in particular for use in treatment of cancer.

The patent (see paragraphs [0031]-[0039]) refers to the importance of predictable conjugation results for the potency, circulating half-lives, target binding and toxicity of antibody-drug-conjugates and teaches in this context that the claimed invention allows for the provision of antibody-drug-conjugates with advantageous homogeneity in terms of site-specificity and stoichiometry and stability. The patent (see examples 32-37 in paragraphs [0348]-[0354] and Figures 22 and

24-30) further presents experimental results substantiating the therapeutic utility of examples of conjugates as defined according to the main request in terms of stability, *in vitro* toxicity, blood clearance, biodistribution and *in vivo* reduction of tumor volume in a mouse xenograft model.

6.2 Starting point in the prior art

6.2.1 Document D52 describes conjugates of the cytotoxin calicheamicin with the anti-C33 murine antibody P67.6 for use in treatment of acute myeloid leukemia (AML). The document describes these conjugates as prepared by linking the cytotoxin to the glycan structure of the antibody by oxidative cleavage followed by hydrazone ligation and reports that these conjugates have shown potent, specific antitumor activity in models of AML (see D52, page 48, Figure 1 and bridging section between left and right column).

In view of their mentioned purpose and structure the Board considers that these conjugates described in document D52 represent a suitable starting point in the prior art with respect to the subject-matter claimed according to the main request.

6.2.2 Document D13 describes a variety of methods for remodeling and labeling proteins and antibodies (see D13, paragraph [007]), including methods for labeling an antibody which may involve the transfer of a sugar with a "chemical handle" to a terminal GlcNAc moiety on the antibody and which may involve prior cleaving of the glycan on the antibody to leave the GlcNAc group appended to the antibody (see D13, paragraphs [0013]-[0018] and [0053]-[0054]). Such methods may in particular involve the use of Endo-H to cleave a

GlcNAc-GlcNAc linkage and Y289L mutant GalT to transfer GalNAz or the use of Endo-M or Endo-A, which are described as capable of the glycan cleavage as well as the transfer, with subsequent conjugation of the sugar linked azide with an alkyne-linked reporter molecule by click chemistry (see D13, paragraphs [0180] and [0182]). Such method is exemplified for chicken anti-goat IgG and goat IgG antibodies labelled with a TAMRA-alkylene detection kit (see D13, paragraphs [0206] and [0226]: examples 2 and 15). Without actual exemplification document D13 further mentions the possible use of a therapeutic antibody such as trastuzumab (see D13, paragraph [00114]), the possible use of a cytotoxin as label or tag to an IgG antibody (see D13, paragraph [00132]) and the possible conjugation by click reaction involving cycloaddition between the azide and a cyclooctyne (see D13, paragraph [0068]).

In the decision under appeal document D13 was regarded as the closest prior art with respect claim 10 of the then auxiliary request 3, which related to similar subject-matter as defined according to the main request.

6.2.3 Document D12 describes the labeling of terminal GlcNAc moieties in antibodies with GalNAz using a GalT-enzyme, in particular GalT(Y289L), to allow for subsequent conjugation of reporter or carrier molecules via click chemistry, wherein the terminal GlcNAc moiety may be generated by enzymatic truncation using Endo-H (see D12, paragraph [0115] and Figure 11B; see also example 26 in paragraph [0275]). Document D12 mentions a variety of possible carrier molecules, including "a drug" as well as the possible use of cyclooctynes for

the click reaction with the azide (see D12, paragraphs [0075] and [0077]).

However, document D12 does not mention conjugates of antibodies specifically binding cancer antigen nor conjugates with a cytotoxin. The Board therefore considers document D12 to represent a less suitable starting point in the prior art than document D13.

6.2.4 Document D23 refers to problems with standard antibody labeling techniques. Conjugation involving amino acid residues of the antibody were problematic due to loss of binding affinity or structural integrity of the antibody. Known chemical labeling via oxidative modification of antibody sugars followed by reductive amination required multiple steps involving harsh reaction conditions and resulted in antibody dependent labeling efficiency.

Document D23 presents in this context click chemistry-mediated antibody labeling methods involving metabolic or enzymatic incorporation of azide-modified sugars into the glycan moiety of the antibody followed by labeling using mild copper-free click reaction conditions. Document D23 describes specifically the labelling of a pAKT antibody involving Endo F2 treatment leaving the GlcNAc residue bound to the asparagine residue of the antibody, enzymatic GalNAz-transfer and biotin alkyne linking by click chemistry followed by conjugation with SA-Qdot 625. Document D23 reports *in vitro* results indicating that the click labeling of the antibodies does not affect their binding activity (see D23, Figure 3).

During the appeal proceedings only opponent 1 relied on document D23 as starting point in the prior art for an

objection of lack of inventive step against the subject-matter of the main request. Opponent 1 presented this objection in the appeal proceedings for the first time with the letter of 14 July 2023, which was well after the the Board's summons to oral proceedings and its communication pursuant to Article 15(1) RPBA. Opponent 1 maintained that the objection had already been presented with its general statement "We consider that each of documents D12, D23 and D12 represent a suitable starting point for inventive step" in its written submission of 10 December 2020 (page 4, item 13) filed during the first instance proceedings, which was included as annex 4 in its reply to the appeal. The Board notes, however, that according to Article 12(3) RPBA the reply to the appeal shall contain the respondent's complete appeal case specifying expressly all the requests, facts, objections, arguments and evidence relied on. As the reply by opponent 1 to the appeal expressly relied for the objection of lack of inventive step against the subject-matter of the main request only on documents D13 and D12 as closest prior art (see the reply, page 9) the Board considers that opponent 1 cannot rely for the introduction of the objection starting from document D23 in the appeal proceedings on the general and unsubstantiated statement regarding document D23 in annex 4 of the reply. This objection is therefore covered by the provision of Article 13(2) RPBA.

As discussed in section 5.2 above, document D23 does not explicitly mention any therapeutic utility of the mentioned conjugates nor describe any experimental results involving the relevant conjugates that would imply their therapeutic utility. Taking account of the purpose of the conjugates as defined in the claims of the main request the Board therefore considers that the

objection starting from document D23 *prima facie* lacks relevance. Accordingly, the Board does not recognize any exceptional circumstances justified with cogent reasons for taking the late filed objection into account and has therefore decided not to admit the objection into the appeal proceedings under Article 13(2) RPBA.

6.3 Differences with the prior art

6.3.1 In the conjugates of document D52 the cytotoxin is conjugated to the antibody via an oxidized glycan by hydrazone ligation. In contrast, in the conjugates of the main request the cytotoxin is conjugated to the antibody by click reaction chemistry of a cycloalkyne group linked to the cytotoxin with an azide group linked to a sugar derivative S (defined in paragraph [0063] of the patent as a derivative of a monosaccharide) which on its turn is linked to the core GlcNAc of the antibody.

6.3.2 The difference between the subject-matter of the main request and the generic teaching in document D13 concerns the implementation of one out of several described antibody labelling strategies (see D13, paragraphs [0180] and [0182]), the selection of a conjugate of an anti-cancer antibody with a cytotoxin and the actual use in therapy. With respect to any specific examples in document D13 (see for instance examples 2 and 15 in paragraphs [0206] and [0226]), this implementation involves the selection of the type of antibody, the selection of a cytotoxin as linked agent, the use of a cylcolalkyne for linking the cytotoxin and the actual utilisation in therapy.

6.4 The objective technical problem

6.4.1 As discussed in section 6.1 above, the patent substantiates the suitability of the defined conjugates for therapeutic use and indicates that the claimed invention is aimed at optimized conjugates for therapeutic application in terms of *inter alia* homogenicity, pharmacokinetics, stability, toxicity and efficacy.

The post-published experimental results in document D51 confirm that conjugates in accordance with the main request (see D51, page 7, Table 1: TA-1/2/3, TM-1/2/3 and BA-1/2/3) indeed exhibit with respect to conjugates resulting from oxidation-hydrazone ligation (see D51, Table 1, TA-7, TM-7 and BA-7) as well as conjugates resulting from linking an azide-modified suger to terminal N-acetylglucosamine residues of untrimmed antibodies (see D51, Table 1: TA-4/5/6, TM-4/5/6 and BA-4/5/6) optimized characteristics in terms of *inter alia* homogenicity, reduced Fc-gamma binding, reduced susceptibility to elastase cleavage, pharmacokinetic profile and *in vivo* efficacy (see D51, pages 30-38, "Results").

Taking account of the disclosure of the invention in the patent the Board considers that the effects described in document D51 are encompassed by the technical teaching and embodied by the disclosed invention and may in accordance with the principles confirmed in G 2/21 (see section 94) be relied upon by the proprietor for inventive step.

6.4.2 The opponents contested that any effect reported in document D51 could be achieved over the whole scope of the claims of the main request due to the generic

structural definitions of the conjugates, in particular as regards the linker, the cytotoxin and the antibody.

The Board observes, however, that from the summary in Table 1 of document D51 it is evident that

- the effects reported in document D51 have been obtained by comparison of examples of conjugates as claimed according to the main request with conjugates which only differ from those claimed in that the conjugation results from linking the azide-modified sugar to terminal GlcNAc residues of untrimmed antibodies as covered by the teaching of document D13 or from oxidation-hydrazone ligation as described in document D52

- the effects are consistently obtained when two different antibodies, two different cytotoxins and three different linkers are used.

In the light of the evidence presented in document D51 the opponents' objection that the effects are not obtained within the whole scope of the claims remains a mere allegation and is consequently not considered convincing.

The opponents' further argument, that no improvement has been demonstrated by any comparison to a specific conjugate of a disclosed example in document D13, is in this context also not considered convincing, because document D13 does not disclose any actual example of a conjugate for therapeutic use suitable for such comparison.

Accordingly, the Board considers that the results reported in document D51 adequately substantiate that

the claimed conjugates are associated with advantageous effects and that these effects originate from the difference of the claimed conjugates with the prior art.

6.4.3 Having regard to the effects demonstrated in document D51 the Board therefore concludes that in view of document D52 as well as document D13 as starting point in the prior art the objective technical problem may be formulated as the provision of optimized glycan linked conjugates of a cancer antigen binding antibody with a cytotoxin for use in therapy.

6.5 Assessment of the solution

6.5.1 As discussed in section 6.2 above, the teaching in documents D12, D13 and D23 includes the preparation of modified antibodies by trimming their glycan moieties to the leave terminal GlcNac groups, which may be the core GlcNAc groups, followed by transfer of a sugar which may carry an azide group allowing subsequent conjugation by click reaction. Moreover, document D41 also describes the remodeling of an antibody involving the trimming of its glycan moiety to leave a single GlcNac group followed by transfer of an oligosaccharide which may be tagged to allow conjugation of a functional component by click reaction (see D41, claims 37-46).

Documents D12, D13 and D23 address the need for antibodies with tags or labels at sites not affecting the binding region which can be conveniently prepared (see D12, paragraph [008]; D13, paragraph [006], D23, left column under "Introduction"). Documents D12 and D13 also address the need for antibodies with post-translational modifications resembling human antibodies

(see D12, paragraph [008]; D13, paragraph [006]). Document D41 refers in a similar manner to the need for consistent glycosylation of antibodies to avoid undesired immune responses and to confer stability and effector activity as well as regulatory compliance (see D41, paragraph [0012]).

However, none of documents D12, D13, D23 or D41 thereby specifically addresses the further optimization of glycan linked conjugates of antibodies specifically binding cancer antigen with a cytotoxin for use in therapy.

In this context the Board observes that the prior art presented a variety of alternative conjugation methods, including the metabolic method described in document D23. The mild preparation conditions and site-specificity mentioned for the enzymatic method in document D23 would therefore not compel the skilled person to pursue conjugates from trimmed antibodies for use in therapy as defined according to the main request, such that their optimized properties for use in therapy as demonstrated in document D51 would merely represent a bonus effect from what was anyway obvious.

6.5.2 Document D66 describes the site-specific and homogenous conjugation of a cytotoxin to the Q295 glutamine of the heavy chain of an cancer antigen binding antibody and additionally the Q297 glutamine in a N297Q mutant using a bacterial transglutaminase (see D66, page 9996, Figure 2). The investigations reported in documents D70-D72 (see abstracts) are also aimed at providing homogenous and stable conjugates of cancer antigen binding antibodies with cytotoxins via direct linking to amino acid residues of the antibodies.

In contrast, the conjugates described in documents D52 and D13 involve conjugation via the glycan moiety of the antibody.

The Board considers that the skilled person would for the further optimization of therapeutically useful glycan linked antibody conjugates not consult documents D66 or D70-D72 describing the site-specific and stable linking to an amino acid residue and that in case of such consultation the skilled person would from such information on amino acid linked conjugates not derive any suggestion regarding the further optimization of glycan linked conjugates.

6.5.3 Document D73 reviews the field of conjugates of antibodies with cytotoxic drugs an mentiones selective conjugation via the glycan moiety by oxidation and hydrazone linkage amongst methods for providing site specific conjugates (see page 335, right column.

The Board finds therein no suggestion towards the further optimization of glycan linked conjugates of cancer antigen binding antibodies with cytotoxins as provided by the conjugates of the main request.

6.5.4 Accordingly, the Board considers that no prior art provided the skilled person with a reasonable expectation that the subject-matter as claimed according to the main request would solve the identified objective technical problem.

The Board therefore concludes that the subject-matter defined in the claims of the main request involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain a patent on the basis of claims 1-8 of the main request filed as auxiliary request 1 with the statement of grounds of appeal and a description to be adapted thereto.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated