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Datasheet for the decision of 18 November 2021

Case Number: T 0578/17 - 3.3.04

Application Number: 09739983.6

Publication Number: 2282773

IPC: A61K39/395, C12N5/02, C07K16/00

Language of the proceedings: EN

Title of invention:
Methods and compositions for making antibodies and antibody derivatives with reduced core fucosylation

Patent Proprietor:
Seattle Genetics, Inc.

Opponent:
Dörries, H. Ulrich/df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB

Headword:
Antibodies with reduced core fucosylation/SEATTLE GENETICS

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2), 123(3), 114(2)

Keyword:

Late submitted material - correct exercise of discretion (yes)
Amendments - added subject-matter (no) - broadening of claim (no)
Claims - clarity after amendment (yes)
Novelty - main request (yes)
Inventive step - main request (yes)
Sufficiency of disclosure - main request (yes)

Decisions cited:

G 0002/88, G 0002/93, G 0003/14

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0578/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 18 November 2021

Appellant: (Patent Proprietor)	Seattle Genetics, Inc. 21823 30th Drive, S.E. Bothell, WA 98021 (US)
Representative:	Abel & Imray Westpoint Building James Street West Bath BA1 2DA (GB)
Appellant: (Opponent)	Dörries, H. Ulrich/df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Fünf Höfe Theatinerstrasse 16 80333 Munich (DE)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 January 2017 concerning maintenance of the European Patent No. 2282773 in amended form**

Composition of the Board:

Chair	L. Bühler
Members:	A. Schmitt
	B. Rutz

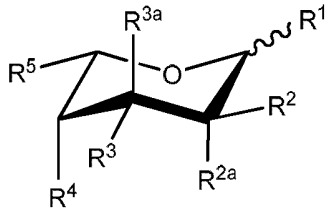
Summary of Facts and Submissions

I. The appeals lodged by the patent proprietor (appellant I, "proprietor") and the sole opponent (appellant II, "opponent") lie from the opposition division's interlocutory decision that European patent No. 2 282 773 ("patent"), as amended in the form of auxiliary request 5, and the invention to which it relates meet the requirements of the EPC.

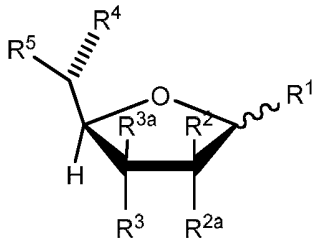
II. The patent, entitled "*Methods and compositions for making antibodies and antibody derivatives with reduced core fucosylation*", was granted on European patent application No. 09 739 983.6, which had been filed as an international application under the PCT published as WO 2009/135181 ("application").

Claim 1 as granted reads as follows:

"1. A method of making a modified antibody or antibody derivative having reduced core fucosylation, comprising:
culturing a host cell in a culture medium comprising an effective amount of a fucose analog under suitable growth conditions, wherein the host cell expresses the antibody or antibody derivative having an Fc domain having at least one complex N-glycoside-linked sugar chain bound to the Fc domain through an N-acetylglucosamine of the reducing terminal of the sugar chain, and
isolating the antibody or antibody derivatives from the cells,
wherein the fucose analog is selected from the group consisting of one of the following formulae (**III**) or (**IV**):



(III)



(IV)

or a biologically acceptable salt or solvate thereof, wherein each of formula (**III**) or (**IV**) can be the alpha or beta anomer or the corresponding aldose form;

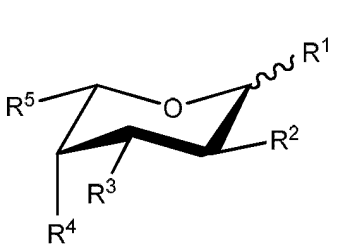
each of R^1-R^4 is independently selected from the group consisting of fluoro, chloro, -OH, -OC(O)H, $-OC(O)C_1-C_{10}$ alkyl, $-OC(O)C_2-C_{10}$ alkenyl, $-OC(O)C_2-C_{10}$ alkynyl, -OC(O)aryl, -OC(O)heterocycle, $-OC(O)C_1-C_{10}$ alkylene(aryl), $-OC(O)C_2-C_{10}$ alkenylene(aryl), $-OC(O)C_2-C_{10}$ alkynyl(aryl), $-OC(O)C_1-C_{10}$ alkylene heterocycle, $-OC(O)C_2-C_{10}$ alkenylene(heterocycle), $OC(O)C_2-C_{10}$ alkynyl heterocycle, $-OCH_2OC(O)$ alkyl, $-OCH_2OC(O)O$ alkyl, $-OCH_2OC(O)$ aryl, $-OCH_2OC(O)O$ aryl, $-OC(O)CH_2O(CH_2CH_2O)_nCH_3$, $-OC(O)CH_2CH_2O(CH_2CH_2O)_nCH_3$, -O-tri-$C_1$-$C_3$ alkylsilyl and $-OC_1-C_{10}$ alkyl, wherein each n is an integer independently selected from 0-5; and each of R^{2a} and R^{3a} is independently selected from the group consisting of H, F and Cl;

R^5 is selected from the group consisting of $-CH_3$, $-CHF_2$, $-CH=C=CH_2$, -C≡CH, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-C(O)OCH_3$, $-CH(OAc)CH_3$, -CN, $-CH_2CN$, $-CH_2X$ (wherein X is Br, Cl or I), and methoxiran;

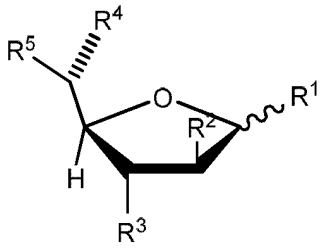
wherein when R^5 is other than $-CH=C=CH_2$ or$-CHF_2$, at least one of R^1, R^2, R^3, R^{2a} and R^{3a} is fluoro or chloro; and

wherein the antibody or antibody derivative has reduced core fucosylation compared to the antibody or antibody

derivative from the host cell cultured in the absence of the fucose analog;
or wherein the fucose analog is selected from the group consisting of one of the following formulae (**I**) or (**II**):



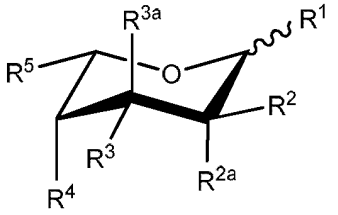
(I)



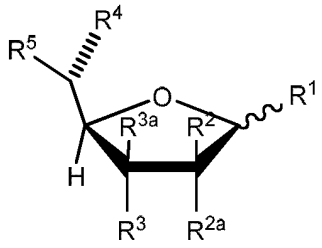
(II)

or a biologically acceptable salt or solvate thereof, wherein:
each of formula (**I**) or (**II**) can be the alpha or beta anomer or the corresponding aldose form;
each of R^1-R^4 is independently selected from the group consisting of -OH, -OC(O)H, -OC(O)C_1-C_{10} alkyl, -OC(O)C_2-C_{10} alkenyl, -OC(O)C_2-C_{10} alkynyl, -OC(O)aryl, -OC(O)heterocycle, -OC(O)C_1-C_{10} alkylene(aryl), -OC(O)C_2-C_{10} alkenylene(aryl), -OC(O)C_2-C_{10} alkynyl(aryl), -OC(O)C_1-C_{10} alkylene heterocycle, -OC(O)C_2-C_{10} alkenylene(heterocycle), -OC(O)C_2-C_{10} alkynyl heterocycle, -OCH_2OC(O) alkyl, -OCH_2OC(O)O alkyl, -OCH_2OC(O) aryl, -OCH_2OC(O)O aryl, -OC(O)$CH_2O(CH_2CH_2O)_nCH_3$, -OC(O)$CH_2CH_2O(CH_2CH_2O)_nCH_3$, -O-tri-$C_1$-$C_3$ alkyl silyl, and -OC_1-C_{10} alkyl, wherein each n is an integer independently selected from 0-5; and
R^5 is selected from the group consisting of -C≡CH, -C≡CCH_3, - CH_2C≡CH, -C(O)OCH_3, -CH(OAc)CH_3, -CN, -CH_2CN, -CH_2X (wherein X is Br, Cl or I), and methoxiran; and wherein the antibody or antibody derivative has reduced core fucosylation compared to the antibody or antibody

derivative from the host cell cultured in the absence of the fucose analog;
or wherein the fucose analog is selected from the group consisting of one of the following formulae (**V**) or (**VI**):



(V)



(VI)

or a biologically acceptable salt or solvate thereof, wherein each of formula (**V**) or (**VI**) can be the alpha or beta anomer or the corresponding aldose form;
each of R^1, R^2, R^{2a}, R^3 and R^4 is independently selected from the group consisting of -OH, -OC(O)H, -OC(O)C_1-C_{10} alkyl, -OC(O)C_2-C_{10} alkenyl, -OC(O)C_2-C_{10} alkynyl, -OC(O)aryl, -OC(O)heterocycle, -OC(O)C_1-C_{10} alkylene(aryl), -OC(O)C_2-C_{10} alkenylene(aryl), -OC(O)C_2-C_{10} alkynyl(aryl), -OC(O)C_1-C_{10} alkylene heterocycle, -OC(O)C_2-C_{10} alkenylene(heterocycle), -OC(O)C_2-C_{10} alkynyl heterocycle, -OCH_2OC(O) alkyl, -OCH_2OC(O)O alkyl, -OCH_2OC(O) aryl, -OCH_2OC(O)O aryl, -OC(O)$CH_2O(CH_2CH_2O)_nCH_3$, -OC(O)$CH_2CH_2O(CH_2CH_2O)_nCH_3$, -O-tri-$C_1$-$C_3$ alkylsilyl, -OC_1-C_{10} alkyl, and a small electron withdrawing group, wherein each n is an integer independently selected from 0-5;
R^5 is a member selected from the group consisting of -CH_3, -CH_2X, -CH(X')-C_1-C_4 alkyl unsubstituted or substituted with halogen, -CH(X')-C_2-C_4 alkene unsubstituted or substituted with halogen, -CH(X')-C_2-C_4 alkyne unsubstituted or substituted with halogen, -CH=C(R^{10})(R^{11}), -C(CH^3)=C(R^{12})(R^{13}),

$-C(R^{14})=C=C(R^{15})(R^{16})$, $-C_3$ carbocycle unsubstituted or substituted with methyl or halogen, $-CH(X')-C_3$ carbocycle unsubstituted or substituted with methyl or halogen, C_3 heterocyle unsubstituted or substituted with methyl or halogen, $-CH(X')-C_3$ heterocycle unsubstituted or substituted with methyl or halogen, $-CH_2N_3$, $-CH_2CH_2N_3$, and benzyloxymethyl, or R^5 is a small electron withdrawing group; wherein

R^{10} is hydrogen or C_1-C_3 alkyl unsubstituted or substituted with halogen;

R^{11} is C_1-C_3 alkyl unsubstituted or substituted with halogen;

R^{12} is hydrogen, halogen or C_1-C_3 alkyl unsubstituted or substituted with halogen; and

R^{13} is hydrogen, or C_1-C_3 alkyl unsubstituted or substituted with halogen;

R^{14} is hydrogen or methyl;

R^{15} and R^{16} are independently selected from hydrogen, methyl and halogen;

X is halogen; and

X' is halogen or hydrogen; and

additionally, each of R^1, R^2, R^{2a}, R^3 and R^{3a} are optionally hydrogen; optionally two R^1, R^2, R^{2a}, R^3 and R^{3a} on adjacent carbon atoms are combined to form a double bond between said adjacent carbon atoms; and

provided that at least one of R^1, R^2, R^{2a}, R^3, R^{3a}, R^4 and R^5 is a small electron withdrawing group, or R^5 comprises a halogen, site of unsaturation, carbocycle, heterocycle or azide, except when (i) R^2 and R^{2a} are both hydrogen, (ii) R^3 and R^{3a} are both hydrogen, (iii) R^1 is hydrogen, (iv) a double bond is present between said adjacent carbon atoms, or (v) R^5 is benzyloxymethyl; and

wherein the antibody or antibody derivative has reduced core fucosylation compared to the antibody or antibody

derivative from the host cell cultured in the absence of the fucose analog."

Claim 24 as granted reads as follows:

"24. A mammalian cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation, comprising an effective amount of a fucose analog, wherein the fucose analog is selected from the group consisting of [one of the formulae (**III**) or (**IV**), or one of the formulae (**I**) or (**II**), or one of the formulae (**V**) or (**VI**), all formulae as defined in claim 1 as granted]."

Claims 36, 81 and 91 of the application each relates to a mammalian cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation comprising an effective amount of a fucose analogue with, in claim 36, the fucose analogue being selected from the group consisting of one of the formulae (**I**) or (**II**); in claim 81, the fucose analogue being selected from the group consisting of one of the formulae (**III**) or (**IV**); and in claim 91, the fucose analogue being selected from the group consisting of one of the formulae (**V**) or (**VI**), all formulae as defined in claim 1 as granted (see above).

III. With the notice of opposition, the patent was opposed under Article 100(a) EPC on the grounds of lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC. In a subsequent letter, the opponent argued lack of novelty (Article 54 EPC).

IV. The opposition division decided, *inter alia*, that claim 21 of the main request and claims 21, 19, 15 and 10 of auxiliary requests 1 to 4, respectively, all

of which were filed with the letter of 8 September 2016, did not meet the requirements of Articles 123(2) and (3) and 84 EPC. The set of claims of auxiliary request 5 was considered to meet the requirements of the EPC.

Claim 1 of the main request and auxiliary request 5 is identical to claim 1 as granted (see section II.).

Claim 21 of the main request is identical to claim 24 as granted (see section II.) except that the claimed mammalian cell culture medium is further defined as "comprising a mammalian cell or cell line that expresses an antibody or derivative thereof".

V. With their statement of grounds of appeal, the proprietor maintained the main request underlying the decision under appeal (see section IV.) and submitted sets of claims of auxiliary requests 1 to 19. They submitted, *inter alia*, arguments to the effect that claim 21 of the main request met the requirements of Articles 123(2) and (3), 84, 54, and 56 EPC and argued that the opposition division "*erred in exercising its discretion to admit late-filed documents D3, D17 to D30 and Annexes A-H into the proceedings*".

VI. With their statement of grounds of appeal, the opponent submitted a document (D33) and argued that the subject-matter of claims 21 to 23 and 26 of the main request was not novel, that no inventive step was required "*to arrive at the teaching of the opposed patent*" (section V.5.33 of the statement of grounds of appeal) and that the invention as defined in the claims of the main request was not sufficiently disclosed.

VII. With their reply to the opponent's statement of grounds of appeal, the proprietor submitted arguments in favour of inventive step and sufficiency of disclosure in relation to the set of claims of the main request.

VIII. With their reply to the proprietor's statement of grounds of appeal, the opponent submitted arguments on the admittance of documents D3, D17 to D30 and Annexes A to H. They further contested that, *inter alia*, claim 21 of the main request met the requirements of Articles 123(2) and (3), 84, and 56 EPC and submitted seven documents, D34 to D40.

IX. With a further letter, the proprietor submitted, *inter alia*, copies of the sets of the claims of auxiliary requests 1 to 4 with the amendments highlighted.

X. As requested by the parties, the board appointed oral proceedings, summoning the parties and issuing a communication pursuant to Article 15(1) RPBA in which it provided its preliminary opinion that the opposition division had correctly exercised its discretion to admit documents D3, D17 to D30 and Annexes A to H into the proceedings; that claim 1 of the main request met the requirements of Articles 56 and 83 EPC; and that claim 21 of the main request met the requirements of Articles 123(2) and (3), 84, 54, 56, and 83 EPC.

XI. In response to the board's communication, the opponent withdrew their request for oral proceedings and stated that they would not attend the oral proceedings.

XII. In response to the opponent's withdrawal of their request for oral proceedings, the proprietor inquired whether the appeal proceedings could be continued in

writing in view of the board's preliminary opinion that the main request met the requirements of the EPC.

XIII. The board cancelled the oral proceedings and informed the parties that the appeal proceedings would be continued in writing.

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

D12 WO 2008/052030

D13 Imai-Nishiya *et al.* 2007, BMC Biotechnol. 7, 84

D14 Sufrin *et al.* 1980, J. Med. Chem. 23(2), 143-149

D15 Winterbourne *et al.* 1979, Biochem. Biophys. Res. Commun. 87(4), 989-992

D22 Sawa *et al.* 2006, Proc. Natl. Acad. Sci. 103(33), 12371-12376

D26 Varki, A. *et al.* 1999, editors, "Chapter 40 Natural and Synthetic Inhibitors of Glycosylation" in "Essentials of Glycobiology", Cold Spring Harbor Laboratory Press

D28 Greene *et al.* 1991, "Reactivities, Reagents, and Reactivity charts" in "Protective Groups in Organic Synthesis", John Wiley & Son, 2nd Ed., 406-416

D30 Maeda *et al.* 2008, Chem Eur. J., 14, 478-487

D32 Lemke *et al*. (editors) 2008, Excerpt from Chapter 10 "Drug Metabolism" in Foye's Principles of Medicinal Chemistry, Wolters Kluwer Lippincott Williams & Wilkins, 6th Ed., 277

D35 Definition of "cell line" and "cell" by The Free Dictionary by Farlex 2017, http://medical-dictionary. thefreedictionary.com/cell+line

D36 Primary Cells vs Cell Lines, 2017, http:// www.lonza.com/products-services/bio-research/ primary-cells/primary-cells-vs-cell-lines

X5 Declaration by Dr Stephen Alley

XV. The proprietor's arguments, where relevant to the decision, are summarised as follows.

Admittance of documents (Article 114(2) EPC)

The documents submitted by the opponent after the expiry of the opposition period (documents D3, D17 to D30 and Annexes A to H) should not have been admitted into the opposition proceedings. Only one of these documents was cited in the opposition division's decision, and neither of the documents was suitable to establish the common general knowledge of the skilled person. Furthermore, the decision of the opposition division to admit these documents was not sufficiently reasoned. The opposition division thus did not exercise its discretion to admit late-filed documents within the correct limits in accordance with Article 114(2) EPC.

Main request

Claim construction

The patent taught methods of making modified antibodies having "reduced core fucosylation" by adding fucose analogues to the culture medium of antibody-expressing cells. An antibody fucosylated with a fucose analogue was also a fucosylated antibody. Antibodies with "reduced core fucosylation" hence had a reduced level of any fucose moiety, including fucose analogues, at the core of the sugar chains. Consequently, the term "reduced core fucosylation" did not include the mere replacement of a fucose attached to the core of the sugar chains with a fucose analogue.

Added subject-matter (Article 123(2) EPC) - claim 21

The subject-matter of claim 21 was directly disclosed in claims 36, 81 and 91 and paragraph [0120] of the application. A mammalian cell or cell line that expressed an antibody or antibody derivative and was contained within a culture medium was further disclosed in paragraphs [0124] and [0127] of the application. An implicit disclosure of the subject-matter of claim 21 was further present in the passages of the application that described the addition of the fucose analogue to the host cell media and referred to the host cells taking up the fucose analogue or to the cell culturing process (paragraphs [0009], [0060], [0128] and [0130]). Claim 21 thus met the requirements of Article 123(2) EPC.

Extension of scope (Article 123(3) EPC) - claim 21

The scope of claim 21 of the main request fell entirely within the scope of claim 24 as granted because it retained all the features of claim 24 and merely comprised the additional feature "mammalian cell or cell line that expresses an antibody or derivative thereof". Adding this further feature to the cell culture medium of claim 24 as granted in fact narrowed the scope of the claim. A cell culture medium comprising a cell might also be called a "cell culture" by the skilled person. However, this merely amounted to the use of an alternative term for the same composition. Thus, neither the claim category nor the sub-class of the claim category was changed by the amendment. Consequently, claim 21 of the main request met the requirements of Article 123(3) EPC.

Clarity (Article 84 EPC) - claim 21

The only new feature contained in claim 21 which had not been present in claim 24 as granted was that the cell culture medium comprised a mammalian cell or cell line that expressed an antibody or antibody derivative. The addition of a mammalian cell or cell line to a cell culture medium did not prevent the claimed entity from being a cell culture medium. The physical entity of the claim was not changed by the amendment and hence the amendment did not add a lack of clarity. The requirements of Article 84 EPC were thus met.

Novelty (Article 54 EPC) - claims 21 to 23 and 26

Since none of the cell culture media disclosed in documents D14, D15 and D22 contained cells that expressed an antibody or antibody derivative, the

subject-matter of claims 21 to 23 and 26 was novel vis-à-vis the disclosure of each of documents D14, D15 and D22.

Inventive step (Article 56 EPC) - claim 1

Document D13 was the most suitable starting point for the assessment of inventive step of claim 1. It disclosed methods of providing antibodies having complex N-glycoside-linked oligosaccharides lacking core fucose. This was achieved by culturing antibody-expressing cells in the presence of siRNAs against genes involved in fucosylation (FUT8, GMD and GFT).

In the method of claim 1 of the main request, the antibody-expressing cells were cultured in the presence of specific fucose analogues. The technical effect of this difference was a simpler, more generally applicable method for producing antibodies having an Fc domain having at least one complex N-glycoside-linked sugar chain bound to the Fc domain and reduced core fucosylation. The examples of the patent provided sufficient evidence that the addition of a fucose analogue as defined in claim 1 to the cell culture medium solved the problem of providing a simpler, more generally applicable method of producing antibodies with reduced core fucosylation.

The claimed solution was not obvious, even when taking into account the disclosure of prior art documents D12, D14 and D15.

In the methods disclosed in document D12, glucosidase or mannosidase inhibitors were added to the culture medium to improve antibody-dependent cellular cytotoxicity (ADCC) and Fc receptor binding. Three of

the tested inhibitors were effective for improving ADCC (Fig. 4 and 5). However, these were not fucose analogues, and they interrupted the early stages of the glycosylation pathway and thus did not produce antibodies with complex N-glycan structures. The only alleged fucosidase inhibitor that was tested (6,8a-diepi-castanospermine) had no effect on CD16 binding (Fig. 4). Moreover, core fucosylation of the expressed antibodies had not been analysed. Document D12 thus did not point towards the claimed solution.

Documents D14 and D15 did not relate to the production of antibodies with reduced core fucosylation. Instead, these documents showed that halogenated L-fucose analogues could enter cells and compete with radio-labelled fucose for incorporation into glycoproteins and glycolipids. Only the global competitive incorporation into macromolecules was analysed. Thus, neither which macromolecules were glycosylated nor whether there was a reduction in fucosylation was examined. It could therefore not be concluded from the disclosure of these documents that administration of halogenated fucose analogues to antibody-producing cells would reduce antibody N-glycan core fucosylation.

Document D12 was not a suitable starting point for the assessment of inventive step because the methods it disclosed did not produce antibodies having complex N-glycoside-linked sugars as required by the method of claim 1. Moreover, the fucose content of the resulting glycoproteins was not analysed. Thus, it was not known whether the methods of document D12 produced antibodies with reduced core fucosylation.

Even if document D12 was selected as a starting point, the combination of the disclosure of document D12 with

the teaching of any of the prior art documents D13, D14 or D15 did not lead to the subject-matter of claim 1 in an obvious manner. Document D13 did not disclose the use of fucose analogues at all, whereas documents D14 and D15 neither related to the production of antibodies with reduced core fucosylation nor taught that halogenated fucose analogues inhibited core fucosylation.

Consequently, the subject-matter of claim 1 of the main request was not obvious in view of the teaching of documents D12, D13, D14 or D15, either taken alone or in combination, and thus it involved an inventive step.

Inventive step (Article 56 EPC) - claim 21

The subject-matter of claim 21 related to a cell culture medium specifically adapted for use in the method of claim 1 and hence involved an inventive step for the same reasons as the subject-matter of claim 1.

Sufficiency of disclosure (Article 83 EPC)

The opponent had not provided any evidence that the scope of the claims included non-working embodiments and thus had not raised serious doubts supported by verifiable facts that the patent enabled the skilled person to achieve a reduced core fucosylation across the whole claimed range.

As regards the fucose analogues, which allegedly were shown in the patent itself to lack activity, it was firstly evident from Table 1 that 5-cyano fucose tetraacetate in pyranose and furanose form had in fact inhibitory activity (entries 8 and 9 on page 39).

Furthermore, the minimal inhibitory activity reported for alkynyl fucose 1,2,3-tri(trimethylacetate) was unusual for this type of compound since the related compounds alkynyl fucose tetrakis(trimethylacetate) and alkynyl fucose di(trimethylacetate) were active as evident from Table 1 of the patent (entries 7 to 10 on page 40). Review of the original source data of the experiment revealed that alkynyl fucose 1,2,3-tri(trimethylacetate) had high inhibitory activity, i.e. Table 1 contained an error (document X5). Thus, when the skilled person used this compound in the claimed method, the core fucosylation of the antibodies was in fact reduced. The claimed invention could hence be carried out with this compound.

The opponent had further questioned whether fluoromethylene fucose tetraacetate could reduce core fucosylation since, according to the patent, it was incorporated into the antibodies at a level of more than 90% (Table 3 of the patent). However, the opponent has not provided any evidence that no inhibition of core fucosylation by this compound occurred. The related fucose analogues chloro-, bromo- and iodo-fucose tetraacetate were all active (Table 1 of the patent, entries 2 to 4 on page 40), and thus, the skilled person would have expected that fluoromethylene fucose tetraacetate also had some inhibitory activity.

Moreover, a broad claimed scope was not as such reason to deny sufficiency of disclosure. The patent's examples provided sufficient evidence that compounds across the whole claimed range had the desired activity of reducing core fucosylation.

In particular, residue R^5 of the Markush formulae of the claims was defined by a relatively short list of

substituents, and the examples of the patent demonstrated the functional activity for most of these substituents.

Furthermore, in view of the teaching in paragraph [0058] of the patent on intracellular metabolites of the fucose analogues, the skilled person would expect that every group at residues R^1 to R^4 that could be deesterified or otherwise converted intracellularly to provide for an OH-group would have activity. The definitions for residues R^1 to R^4 only comprised such -OH structures or esters or ethers/ acetals which could be converted to provide for an -OH group. Only a limited number of "core compounds" following the removal of the R^1 to R^4 ethers or esters were defined in the claims, and many of them were included in the examples, demonstrating their activity in the claimed methods.

Documents D28 and D32 cited by the opponent did not contain any evidence which raised doubts that the invention as defined in the claims could be carried out across its claimed range.

Firstly, most of the ethers disclosed in document D28 did not fall within the scope of claims 1 and 21 and were thus irrelevant. Secondly, the "harsh" conditions in laboratory synthesis disclosed in document D28 were not relevant in a living cell. Thirdly, 1-methyl-2,3,4-triacetyl alkynyl fucose was shown in the patent to be active (Table 1, page 41, line 5) despite having a methyl-ether group at position R^1. This further showed the irrelevance of the disclosure of document D28 for the claimed invention.

Furthermore, document D32 (page 227) taught that dealkylation of ethers was a common metabolic reaction and thus could not support insufficiency of disclosure, either. Deesterification or dealkylation was not even a necessary step in the claimed method.

Finally, the possible substituent groups set out in paragraphs [0025] to [0045] of the patent were conventional in organic chemistry, and no evidence had been provided by the opponent that any of them would present difficulties to the skilled person.

Consequently, the opponent failed to raise serious doubts supported by verifiable facts that the patent enabled the skilled person to achieve a reduced core fucosylation across the whole claimed range. The invention as defined in claims 1 and 21 of the main request was thus sufficiently disclosed.

XVI. The opponent's arguments, where relevant to the decision, are summarised as follows.

Admittance of documents (Article 114(2) EPC)

Documents D3 and D17 to D28 had been submitted in response to arguments in the proprietor's response to the notice of opposition; documents D29, D30 and Annexes A to H had been submitted in response to the opposition division's preliminary opinion. Thus, most of these documents were not "late filed" within the meaning of Article 114(2) EPC. Moreover, many of the documents had been discussed in detail during the oral proceedings, supporting their *prima facie* relevance. Consequently, the opposition division's decision to admit all documents into the proceedings had been correct.

Main request

Claim construction

The patent did not provide a basis for interpreting the expression "reduced core fucosylation" as requiring an inhibition of fucosylation distinct and independent of incorporation of fucose analogues into the antibody. Consequently, "reduced core fucosylation" was also achieved when a fucose analogue was incorporated into the antibody instead of a fucose residue. This view was supported by the examples of the patent, which disclosed that all fucose analogues were also incorporated into the antibodies to different degrees (Table 3) and hence were substrates rather than inhibitors of the fucosyltransferase. The patent therefore did not teach a reduction in fucosylation without incorporation of the fucose analogues.

Added subject-matter (Article 123(2) EPC) - claim 21

The application did not disclose "a cell culture medium comprising a mammalian cell or cell line". Passages of the application that related to the process of culturing a host cell or cell culture assays (paragraphs [0009], [0060], [0124], [0127], [0128] and [0130]) could not serve as a basis for this physical entity because a "cell culture" was not the same as a "culture medium comprising a cell". A cell culture comprised the additional features of culturing and growing cells, which further required that the cells were alive and used up nutrients from and secreted metabolites into the medium. The medium therefore changed over time and needed to be eventually exchanged to further sustain the cells. However, the

subject-matter of claim 21 merely comprised the localisation of cells in a medium and therefore required neither culturing and growing the cells in the medium nor that the cells be alive.

Claim 21 hence related to subject-matter that extended beyond the content of the application, contrary to the requirements of Article 123(2) EPC.

Extension of scope (Article 123(3) EPC) - claim 21

The mammalian cell culture medium as claimed in claim 21 comprised a mammalian cell or cell line not present in the mammalian cell culture medium of claim 24 as granted. This cell or cell line would likely be considered a substantial means for carrying out the claimed invention. This led to situations such as the provision of a mammalian cell or cell line intended or suitable for use in the claimed culture medium which, in accordance with national law, might be considered a contributory infringement of a patent containing claim 21 of the main request, which, however, would not have been considered a contributory infringement of the patent as granted. The scope of protection has thus been broadened.

Moreover, the addition of alive, metabolising cells to a cell culture medium altered the composition of the medium since the cells used up nutrients from and secreted metabolites into the medium. The subject-matter of claim 21 hence encompassed combinations of cells and spent media. This was not encompassed by the subject-matter of claim 24 as granted. Consequently, the scope of claim 21 of the main request was extended compared to the scope of claim 24 as granted, contrary to Article 123(3) EPC.

Clarity (Article 84 EPC) - claim 21

Since a combination of a cell and a cell culture medium as recited in claim 21 was commonly referred to as a "cell culture", it was unclear whether the claimed subject-matter was intended to relate to such a cell culture, i.e. whether the claimed cell culture medium needed to be capable of sustaining further cell growth.

Furthermore, the expression "cell or cell line" lacked conciseness since the terms "cell" and "cell line" overlapped. The term "cell line" further lacked clarity since different definitions for it existed in the state of the art, as evident from documents D35 and D36.

Moreover, the term "antibody derivative" lacked clarity in view of the definitions for the terms "antibody" and "antibody derivative" in paragraphs [0019] and [0020] and the lack of any limit for this term in claim 21. This objection was admissible under the principles established in decision G 3/14 of the Enlarged Board of Appeal (OJ EPO 2015, A102) because in claim 24 as granted, the term "antibody derivative" was not a limiting feature and was further defined as "having reduced core fucosylation", which imposed limitations at least with regard to the existence of fucosylation sites.

Novelty (Article 54 EPC) - claims 21 to 23 and 26

The arguments and submissions during the opposition proceedings on lack of novelty of the subject-matter of claims 21 to 23 and 26 over documents D14 and D15 were maintained in view of the fact that certain compounds

disclosed in documents D14 and D15 fell under one of the formulae recited in claim 21.

Inventive step (Article 56 EPC) - claim 1

The cellular pathways and enzymes for protein glycosylation, including fucosylation, were identical for all glycoproteins, including antibodies. Therefore, the reduction of antibody fucosylation required solving the same problems as for the reduction of fucosylation of other glycoproteins. Consequently, prior art documents on cellular glycosylation and fucosylation pathways and enzymes (documents D14, D15 and D22) must be taken into account for the assessment of inventive step of the subject-matter of claim 1.

It was known in the art that the absence of core fucosylation on antibodies boosted ADCC (document D13, page 2, left-hand column) and that antibodies having complex-type glycan structures had longer serum half-lifes than antibodies of the oligomannose type. The skilled person thus had an interest in producing antibodies with complex-type glycan structures and reduced core fucosylation. Documents D12 and D13 disclosed methods for producing such antibodies, these documents being suitable starting points for the assessment of inventive step.

Document D13 disclosed a method for producing non-fucosylated antibodies with enhanced ADCC by siRNA-dependent knock-down of fucosyltransferases in antibody-producing host cells. The subject-matter of claim 1 differed from this method in that it did not require genetic modification of the host cells but used fucose analogues added to the culture medium as inhibitors of the fucosyltransferases. The technical

effect was that cell engineering was not required. Thus, the objective technical problem was the provision of a method for providing an antibody or antibody derivative having reduced core fucosylation and having at least one complex N-glycoside-linked sugar chain bound to the Fc domain without the need for cell engineering.

The solution provided in claim 1 - the addition of fucose analogues as defined in claim 1 - was obvious in view of prior art documents teaching a similar approach of adding glycosylation inhibitors to cell culture media.

Document D12 disclosed a method for producing antibodies with reduced core fucosylation by adding carbohydrate modifiers to the culture medium of host cells. This was considered to be advantageous over knock-down approaches (paragraph [0009]). Documents D26 ("Introduction" on the first page) and D30 (page 479, top paragraph) confirmed the advantages of glycosylation inhibitors and the interest in inhibitors of fucosyltransferases. The skilled person would thus have considered the use of substrate analogues as inhibitors of the fucosylation enzymes knocked-down in document D13. Such substrate analogues and inhibitors of fucosylation were described in documents D14, D15 and D22.

Document D14 disclosed that halogenated fucose analogues falling within the scope of formulae (I), (III) and (V) of claim 1 were effective in reducing fucosylation by competitive incorporation and inhibiting fucosylation enzymes (abstract, page 143, last paragraph, Table II). The fucose analogue 6-fluoro-fucose was taken up by cells and metabolised to

GDP-6-fucose, a known inhibitor of fucosyl-transferases (Fig. 1 of document D14).

Document D15 also disclosed a fucose analogue falling within the scope of formula (III) and showed both its incorporation into macromolecules and inhibition of fucosylation by this compound (Table, page 990, second-last paragraph to page 991, first paragraph).

It was therefore obvious to the skilled person that the halogenated fucose analogues disclosed in documents D14 and D15 were inhibitors of fucosylation enzymes and that they could be used in a method of making antibodies having reduced core fucosylation.

Moreover, document D22 taught that acetylated 6-azido fucose analogues falling within the scope of formula (V) of claim 1 also reduced core fucosylation through competitive incorporation (page 12374, left-hand column and paragraph bridging the columns; page 12375, right-hand column, first full paragraph; abstract).

Thus, the skilled person would have considered the compounds disclosed in documents D14, D15 or D22 for the inhibition of fucose incorporation into glycoproteins and, based on the fact that the same fucosylation enzymes were involved in the production of all glycoproteins, would have determined, by routine testing, whether those compounds were also able to reduce core fucosylation of antibodies. The claimed subject-matter was thus obvious to the skilled person.

Document D12 also related to the problem of providing antibodies with reduced core fucosylation and disclosed culturing antibody-expressing host cells in the

presence of a carbohydrate modifier. The preferred inhibitor was castanospermine, which reduced core fucosylation by inhibiting early stage glycosylation enzymes, but other glycosylation inhibitors were also taught, including inhibitors of fucosyltransferases (paragraphs [0027] and [0044] to [0048]). While core fucosylation of the antibodies was not analysed and one of the inhibitors showed no effect on ADCC in the concentration tested (paragraph [0119]), a reduction of core fucosylation must nonetheless have taken place in the presence of a fucosyltransferase inhibitor.

The only difference of claim 1 to the teaching of document D12 was thus the use of a different fucosyltransferase inhibitor, which resulted in a measurably reduced core fucosylation of the antibodies.

Since antibodies having complex-type glycan structures had longer serum half-lifes than antibodies lacking this structure and non-fucosylated antibodies had a higher ADCC activity, the skilled person would have searched for late-stage glycosylation inhibitors, in particular fucosylation inhibitors. They would have found them in documents D14, D15 or D22, as shown in the context of discussing document D13 as the closest prior art.

Consequently, the subject-matter of claim 1 also lacked an inventive step in view of the teaching of document D12 in combination with documents D14, D15 or D22.

Inventive step (Article 56 EPC) - claim 21

The subject-matter of claim 21 lacked inventive step for the same reasons as outlined for the subject-matter

of claim 1 and over the documents discussed in detail for claim 1. Thus, in applying this reasoning to claim 21, adding a cell or cell line expressing antibodies to the cell culture medium to produce the antibodies was obvious for the skilled person.

Sufficiency of disclosure (Article 83 EPC)

In accordance with established case law, a patent itself could be used to provide the serious doubts and accompanying verifiable facts to find a lack of sufficiency of disclosure. In the case at hand, the patent disclosed that not all compounds falling within the claimed range could be used to make antibodies with reduced core fucosylation and that therefore the patent did not enable the skilled person to obtain reduced core fucosylation of antibodies with all claimed analogues.

Firstly, Table 3 of the patent (page 42) disclosed that the fucose analogue fluoromethylene fucose or its peracetate were incorporated in more than 90% of the antibodies. This, in the absence of data regarding the status of the remaining 10% of the antibodies, taught the skilled person that for these fucose analogues, only incorporation of the analogues but not inhibition occurred. Fluoromethylene fucose was further known from document D14 (compound 4a), complementing the teaching of the patent and confirming that this fucose analogue was incorporated into macromolecules without effective reduction of core fucosylation.

Furthermore, as disclosed in Table 1 of the patent (page 39, line 41), 5-cyano fucose tetraacetate also had only a minimal inhibitory effect (5-10% at 50 µM).

Moreover, as disclosed in Table 1 of the patent (page 40, line 41), alkynyl fucose 1,2,3-tri(trimethyl-acetate) did not inhibit fucosylation at all, i.e. this compound included in the scope of claims 1 and 21 did not work.

The late-filed evidence submitted by the proprietor during the opposition proceedings that a review of the data showed that alkynyl fucose 1,2,3-tri(trimethyl-acetate) reduced core fucosylation by more than 80% was not available to the skilled person at the filing date of the application. Since sufficiency of disclosure had to be judged on the basis of the information accessible to the skilled person at the filing date taking into account the common general knowledge (decision G 2/93 of the Enlarged Board of Appeal, OJ EPO 1995, 275), this late-filed evidence could not be taken into account. The skilled person thus had no reason to be sceptical of the teaching of the patent that alkynyl fucose 1,2,3,tri(trimethylacetate) was inactive or toxic at both concentrations tested.

Moreover, the claims covered millions of compounds since the formulae allowed for a large variety of substituents in positions R^5 and R^1 to R^4, but only a few of these were shown to be effective (Table 1). According to paragraphs [0025] to [0045] of the patent, the terms "alkyl", "alkenyl", "aryl" and others used in the claims allowed for further substitutions which were not exemplified in the patent and would not be expected to be functional.

In particular, the skilled person would not expect compounds comprising large ester or ether groups in positions R^1 to R^4 to be functional since not all groups defined for R^1 to R^4 in the claims could be

hydrolysed. For example, alkylsilyl groups larger than trimethylsilyl ethers and $-OC_1-C_{10}$ alkyl groups could not be hydrolysed even under harsh conditions, as supported by document D28 (page 414, page 413 for the protective groups corresponding to R^1 to R^4 of the claims, pages 406-411 for reaction conditions and pages 411-412 for interpretation of the table). Hence, these compounds could not be effective.

Furthermore, it was common general knowledge that for drug molecules containing more than one ether group, usually only one was dealkylated enzymatically, and the rate of O-dealkylation was a function of chain length, i.e. increasing chain length or branching reduced the rate of dealkylation (document D32, page 277, paragraph bridging columns). Long branched ethers in positions R^1 to R^4 were covered by the claims, and the patent did not provide any information rendering it plausible that they could effectively inhibit fucosylation in spite of the common general knowledge to the contrary.

Additionally, no clear structure-function relationship for the substitutions in position R^5 existed and, as shown in the patent, minor structural changes at the R^5 position could abolish the inhibitory activity of a compound. It was therefore implausible that the multitude of claimed substituents in the R^5 position, for which no examples were provided in the patent, allowed for inhibition of core fucosylation. Moreover, the skilled person could not determine without undue experimentation which of the millions of claimed compounds not experimentally shown to be effective could be used to obtain an effective reduction in core fucosylation of antibodies.

The lack of examples covering the broad scope of the claims and the serious doubts based on common general knowledge and evidence from the patent itself rebutted any presumption that the teaching of the patent could be carried out without an undue burden, over the whole scope of the claims. The invention as defined in claims 1 and 21 of the main request was thus not sufficiently disclosed.

XVII. The proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request as filed on 8 September 2016 and resubmitted with the statement of grounds of appeal or, alternatively, on the basis of the set of claims of one of auxiliary requests 1 to 19 filed with the statement of grounds of appeal.
They also requested that the opposition division's decision to admit documents D3, D17 to D30 and Annexes A-H be overturned and that these documents be held inadmissible.

XVIII. The opponent requested that the decision be set aside and that the patent be revoked.

Reasons for the Decision

1. The appeals comply with Articles 106 to 108 and Rule 99 EPC and are admissible.

Admittance of documents (Article 114(2) EPC)

2. The proprietor challenged the opposition division's decision to admit all "late filed" documents, i.e. all documents filed after the expiry of the opposition period, into the proceedings. The proprietor argued

that the decision was not reasoned and that "*the Opposition Division exercised its discretion in an unreasonable way, and thus exceeded the proper limits of its discretion*" (section 3.2 of the proprietor's statement of grounds of appeal).

3. Admitting documents into opposition proceedings at a late stage lies within the discretion of the opposition division (Article 114(2) EPC). Absent any convincing reasons for considering the discretion to have been exercised in accordance with the wrong principles or in an unreasonable way, such a decision will not be reversed by a board of appeal. In particular, it is not the function of the board to review all the facts and circumstances of the case as if it were the opposition division (see Case Law of the Boards of Appeal, 9th edition, 2019, IV.C.4.5.2).

4. The opposition division did not give detailed reasons on admittance but only considered the late-filed documents "*as prima facie relevant for the assessment of patentability*" (point 16 of the decision). *Prima facie* relevance is a criterion for admittance and is ascertained on the face of the facts, i.e. with little investigative effort. Moreover, *prima facie* relevance does not require that the new fact or document taken alone prejudice the maintenance of the patent. Rather, the new fact or document must appear to be relevant for the outcome of the case. Relevance has thus to be assessed in relation to facts to be proven.

5. The board notes that documents D3 and D17 to D28 were submitted on 3 February 2016 in response to the proprietor's submission and nine months prior to the oral proceedings. Documents D29, D30 and Annexes A to H were submitted on 8 September 2016 in response to the

communication in accordance with Rule 116 EPC. The documents were thus submitted to back up factual arguments in the opposition brief with which the proprietor disagreed. Moreover, the proprietor had enough time to consider the new facts and to file additional evidence (documents X5, D31 and D32).

6. Thus, the board sees no compelling arguments that the opposition division exercised their discretion according to the wrong principles or, in view of when the documents were filed, in an unreasonable way. The decision of the opposition division to admit these documents into the proceedings is thus not overturned.

Main request

Claim construction

7. The opponent argued that the incorporation of a fucose analogue into an antibody resulted in an antibody with reduced core fucosylation, whereas the proprietor considered that an antibody fucosylated with a fucose analogue was also a "fucosylated antibody".

8. The board holds that antibodies with "reduced core fucosylation" have a reduced number of any fucose moiety, including native fucose and any analogue of (native) fucose, at the complex N-glycoside-linked sugar chain(s). This interpretation is how the skilled person would objectively understand the term "reduced core fucosylation". Paragraphs [0055] and [0056] of the patent, which refer to "*core fucosylation by fucose*" and "*core fucosylation by a fucose analog*", are in line with the common understanding. A "fucosylated antibody" may thus comprise fucose or a fucose analogue, whereas "reduced core fucosylation" means a reduced number of

any fucose moiety, including fucose analogues. Consequently, the mere incorporation of a fucose analogue into an antibody instead of native fucose does not result in an antibody with reduced core fucosylation.

Added subject-matter (Article 123(2) EPC) - claim 21

9. Claim 21 relates to a mammalian cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation, comprising a mammalian cell or cell line that expresses an antibody or antibody derivative and an effective amount of a fucose analogue (see section IV. above).

10. In the decision under appeal, the opposition division considered that the application only disclosed the addition of mammalian cells or cell lines to a cell culture medium but not that the cells were "*comprised in the culture medium itself*" (point 21.3 of the decision). In which case, the skilled person would understand that culture media were used to culture cells but did not comprise cells.

11. The board is unable to follow this reasoning and considers that if cells have been added to a cell culture medium, the medium comprises cells and, equally, if a culture medium is used to culture cells, it has to comprise those cells.

12. Furthermore, it has not been disputed by the parties that the application discloses mammalian cell culture media for the production of antibodies or antibody derivatives having reduced core fucosylation which comprise an effective amount of a fucose analogue as defined in claim 21 (see claims 36, 81 and 91 (see

section II. above) and paragraph [0060] (see point 14. below)).

13. The purpose of antibody production can only be achieved if the medium contains (or comprises) host cells expressing antibodies or antibody derivatives. Suitable host cells are described for example in paragraph [0120] of the application, which discloses that "[a] *variety of mammalian cells and cell lines can be utilized to express an antibody or derivative thereof*".

14. The expression of antibodies by the cells or cell lines likewise requires that these cells are present in a cell culture medium, i.e. that they are "cultured", as described in various sections of the application (paragraphs [0009], [0060], [0120], [0124], [0127]).

Paragraph [0060], for example, describes that "*[s]uitable fucose analogues (identified below as Formula I, II, III, IV, V and VI) are those that* can *be added to the host cell culture media and that inhibit core fucosylation...*". Furthermore, the fucose analogue is "*typically taken up by host cells*". Paragraph [0060] thus discloses a cell culture medium comprising fucose analogues as defined in claim 21 and, if not in plain words then at least implicitly, host cells.

Paragraph [0127] also discloses a combination of the physical entities "mammalian cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation", "a mammalian cell or cell line that expresses an antibody or derivative thereof" and "an effective amount of a fucose analog" as defined in claim 21 because, according to this paragraph, "*the cells expressing the antibody or*

antibody derivative can be cultured by growing the host cell in any suitable volume of culture media supplemented with the fucose analog".

15. The opponent argued that passages of the application that related to the process of culturing a host cell such as paragraphs [0060] and [0127] could not serve as a basis for the physical entity claimed in claim 21 because a "cell culture" was not the same as a "culture medium comprising a cell". The latter merely required the localisation of the cells in a medium whereas the culturing of a cell further encompassed culturing and growing cells, required cells that were alive, and implied that the medium was changed over time during the culturing process.

16. The board is not convinced by this argument either. Rather, it considers that the "cell culture" disclosed in paragraphs [0060] and [0127] of the application describes a product comprising the same features as the product defined in claim 21. The culturing or growing of the cells described in these paragraphs (see point 14. above) is carried out using this product, namely the cell culture medium comprising the cell or cell line and the fucose analogue.

17. The opponent also argued that the subject-matter of claim 21 did not require that the cells in the culture medium be alive. However, in the context of a mammalian cell culture medium for the production of antibodies or antibody derivatives as recited in claim 21, the only technically reasonable interpretation of the feature recited in claim 21 that the mammalian cell or cell line "expresses an antibody or antibody derivative thereof" is that the cell culture medium comprises living cells which actively express these proteins. The

skilled person would thus not understand the subject-matter of claim 21 to encompass a cell culture medium comprising dead cells.

18. In view of the above considerations, the board is of the opinion that the subject-matter of claim 21 has a basis in the application as filed. Consequently, the set of claims of the main request meets the requirements of Article 123(2) EPC.

Extension of scope (Article 123(3) EPC) - claim 21

19. Compared to the subject-matter of claim 24 as granted (see section II.), the subject-matter of claim 21 of the main request (see section IV.) comprises the further feature that the claimed cell culture medium comprises a mammalian cell or cell line that expresses an antibody or antibody derivative.

20. The opponent argued that claim 21 extended the protection it conferred beyond that of claim 24 as granted because the addition of living, metabolising cells to a cell culture medium altered the composition of the medium. Unlike claim 24 as granted, the subject-matter of claim 21 hence encompassed combinations of cells and spent media.

21. The board is not convinced by this argument. The addition of a mammalian cell or cell line to the mammalian cell culture medium changes neither the claim category nor the scope or meaning of the term "mammalian cell culture medium" compared to claim 24 as granted. In both claims, the cell culture medium is further defined as suitable for the production of antibodies or antibody derivatives having reduced core fucosylation. This, in the board's opinion, excludes

"spent media", which are not able to support the production of cellular proteins. The board therefore holds that the same cell culture medium is encompassed by the scope of claim 24 as granted and claim 21 of the main request.

22. The opponent further argued that the addition of the cell or cell line to the cell culture medium led to situations which might be considered an infringement of a patent containing claim 21 of the main request, which, however, would not have been considered an infringement of the patent as granted (see pages 5 to 6 of the opponent's reply to the proprietor's appeal, sections II.2.1 to II.2.7: "*Possible contributory infringement*"). The protection it conferred was thus extended.

23. However, the prohibition under Article 123(3) EPC to amend European patents in a way which extends the protection they confer is a matter which must be decided having regard to the scope of the claims (Article 69(1) EPC) and not the rights conferred by a European patent under national law (Article 64 EPC). It is therefore only required to decide whether the scope of claim 21 of the main request is broader than the scope of any of the claims of the patent as granted. The national law of the contracting states in relation to infringement does not need to be considered when making this decision (see decision G 2/88, OJ EPO 1990, 93, point 3.3 of the Reasons).

24. Consequently, since the board holds that the scope of claim 21 of the main request is not broader than the scope of claim 24 as granted (see point 21. above), claim 21 of the main request meets the requirements of Article 123(3) EPC.

Clarity (Article 84 EPC) - claim 21

25. The opponent argued that a combination of a cell and a medium was commonly referred to as a cell culture. Since this term was not used in claim 21, it was not clear whether the cell culture medium of claim 21 needed to be capable of sustaining further cell growth. This argument fails to convince the board since the cell culture medium as defined in claim 21 of the main request and claim 24 as granted has to be suitable for the production of antibodies or antibody derivatives having reduced core fucosylation and hence needs to be capable of sustaining the cells such that they can produce antibodies (see point 21.).

26. The opponent further objected to the expression "cell or cell line" for lack of conciseness and lack of clarity in view of various definitions existing for this term in the state of the art. The board, however, is of the opinion that "cell" and "cell line" are conventional terms used in the art, the meanings of which are clear to the skilled person in the context of the production of antibodies. The definitions in documents D35 and D36 merely emphasise that different types of cell lines exist, which are all encompassed by the term "cell line" used in claim 21. Furthermore, the use of both terms "cell" and "cell line" in claim 21 merely emphasises that cell lines are encompassed within the scope of the claim. This does not result in a lack of conciseness justifying an objection under Article 84 EPC.

27. Finally, the opponent argued that the term "antibody derivative" lacked clarity in view of the definitions for the terms "antibody" and "antibody derivative" in

paragraphs [0019] and [0020] and the lack of any limit for this term in claim 21. However, the expression "antibody derivative" was already present in claim 24 as granted and thus may not be examined for compliance with the requirements of Article 84 EPC (see decision G 3/14, OJ EPO 2015, A102, Order).

28. The opponent's further argument that the term "antibody derivative" was not a limiting feature in claim 24 as granted does not convince the board. The expression "cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation" imposes a limitation on the cell culture medium in that it has to be suitable for the claimed purpose. Within the claimed purpose, the term "antibody derivative" has a defining and limiting function, irrespective of whether it is further defined as having reduced core fucosylation. The board therefore holds that the term "antibody derivative" in claim 21 may not be examined for compliance with the requirements of Article 84 EPC (see decision G3/14, OJ EPO 2015, A102, Order).

29. Consequently, claim 21 of the main request meets the requirements of Article 84 EPC.

Novelty (Article 54 EPC) - claims 21 to 23 and 26

30. The opponent indicated in their statement of grounds of appeal that they maintained their "*arguments and submissions made during the first instance proceedings that the subject-matter of claims 21-23 and 26 of the Main Request and the corresponding claim(s) of Auxiliary Request 1 to 4 lacks novelty over D14 and D15; see in particular item 5 of our submission of September 8 2016*".

31. It can be left open whether the opponent's objection of lack of novelty is sufficiently substantiated when taking into account the summary on page 2 of their statement of grounds of appeal. In any case, the opponent's submissions made on 8 September 2016 related to different claim requests (filed on 1 June 2015) which notably did not include the feature "comprising a mammalian cell or cell line that expresses an antibody or derivative thereof". Therefore, the opponent's novelty objections submitted on 8 September 2016 do not apply to claims 21 to 23 and 26 of the main request submitted with the proprietor's statement of grounds of appeal.

32. Consequently, in the absence of novelty objections to the claims of the main request, the board holds that the main request meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC) - claim 1

33. Claim 1 is directed to a method of making a modified antibody or antibody derivative having reduced core fucosylation comprising culturing a host cell expressing the antibody or antibody derivative in a culture medium comprising an effective amount of a particular fucose analogue (see section IV.).

34. The opponent assessed inventive step of the claimed subject-matter using either document D12 or D13 as closest prior art and combined the disclosure in these documents with the disclosure in documents D14, D15 or D22 as regards fucosylation of macromolecules with fucose analogues.

35. Document D12 is concerned with cell culturing methods and media for the production of antibodies with improved antibody-dependent cellular cytotoxicity (ADCC) and altered glycosylation pattern (paragraph [0002]). These methods comprise culturing antibody-expressing host cells in the presence of a carbohydrate modifier, including inhibitors of early stage glycosylation enzymes and inhibitors of fucosyltransferases (paragraphs [0027] and [0044] to [0048]). However, in the experiments reported in document D12, core fucosylation of the resulting antibodies was not analysed, and the fucosyltransferase inhibitor that was tested showed no effect on ADCC (paragraph [0119]). The preferred inhibitor, castanospermine, is not a fucosyltransferase inhibitor (paragraphs [0027] and [0048]).

36. Document D13 discloses a method for producing non-fucosylated antibodies with enhanced ADCC by siRNA-dependent knock-down of fucosyltransferases in antibody-producing host cells.

37. Irrespective of the document used as a starting point, the subject-matter of claim 1 of the main request differs from the prior art methods disclosed in documents D12 and D13 at least in that the cell culture medium comprises an effective amount of a fucose analogue as defined in claim 1. This has not been disputed by the parties.

38. Furthermore, irrespective of whether the objective technical problem is formulated as the provision of an alternative method, as suggested by the opponent, or a simpler and thus improved method, as formulated by the proprietor, it has to be established for the assessment of inventive step whether it was obvious to the skilled

person that a reduced core fucosylation of antibodies could be achieved by culturing antibody-expressing cells in a culture medium comprising an effective amount of a fucose analogue as defined in claim 1.

39. The opponent argued that the claimed subject-matter was obvious to the skilled person in view of the teaching of documents D14, D15 or D22, which disclosed inhibition of fucosylation of macromolecules, including glycoproteins, by fucose analogues falling within the definition of the fucose analogues in claim 1. The skilled person, starting from either document D12 or D13 as the closest prior art, "*would have been motivated to at least try and see if the analogues of D14, D15 or D22 were able to reduce fucosylation of antibodies*" (section V.4.34 of the opponent's statement of grounds of appeal). Thus, no inventive step was required to arrive at the claimed subject-matter. In this context, the opponent also referred to documents D26 and D30, which confirmed the skilled person's interest in glycosylation inhibitors and, in particular, inhibitors of fucosyltransferases.

40. The board is not convinced by this line of argument because, in fact, neither document D14, D15 nor D22 discloses an inhibition or reduction of fucosylation of macromolecules, including glycoproteins, by the fucose analogues used in the analyses reported in these documents.

41. Document D14 analyses the effect of halogenated fucose analogues on cell growth and macromolecular biosynthesis in a human mammary tumour cell line. It discloses a reduction ("*inhibition*") in uptake of radioactive fucose into macromolecular components present in an acid-precipitable cell fraction (see

page 145, Table II). However, this type of analysis allows neither identifying the type of fucosylated macromolecule in the cell fraction nor the reasons for the observed reduction in uptake. In fact, competitive incorporation of the halogenated fucose rather than inhibition of fucosylation is suggested in document D14 as the mechanism for the observed reduction (see page 146, right-hand column, second paragraph, which discloses that tritiated compound 4a "*is converted to GDP-6-fluorofucose and eventually incorporated into glycoprotein and glycolipid*"). However, the mere replacement of a fucose moiety in a molecule by a fucose analogue moiety does not result in a reduction of the fucosylation of this molecule (see the claim construction in point 8. above). The skilled person thus cannot draw any conclusions from the disclosure of document D14 with respect to a possible inhibition or reduction of protein fucosylation by any of the halogenated fucose analogues analysed in this document.

42. Document D15 (page 991, last paragraph) discloses that the fluoro-analogue of fucose competes with non-fluorinated fucose in glycoprotein biosynthesis, i.e. it discloses competitive incorporation of the fucose analogue into glycoproteins but is silent as regards an inhibition or reduction of core fucosylation of glycoproteins by this fucose analogue.

43. Likewise, document D22 (page 12375, right-hand column, first full paragraph) discloses that an azido-containing fucose analogue is incorporated into glycoproteins via the fucose salvage pathway but not that it inhibits or reduces core fucosylation of glycoproteins.

44. Thus, neither document D14, D15 nor D22 teaches an inhibition or reduction of the fucosylation of macromolecules, including glycoproteins, by any of the fucose analogues disclosed in these documents.

45. As a consequence, the board holds that the teaching of documents D14, D15 and D22 could not motivate the skilled person, as argued by the opponent, to try to see whether these analogues were able to reduce fucosylation of antibodies since nothing in these documents pointed towards an inhibition or reduction of the fucosylation of glycoproteins by any of the fucose analogues analysed in them. Consequently, irrespective of whether the skilled person had, as suggested by the opponent in view of the teaching of documents D26 and D30, a particular interest in finding inhibitors of fucosyltransferases, it was not obvious to the skilled person that any of the fucose analogues as defined in claim 1 of the main request could inhibit or reduce the fucosylation of glycoproteins, let alone antibodies.

46. In view of these considerations, the board holds that the subject-matter of claim 1 of the main request involves an inventive step, irrespective of whether document D12 or D13 is used as the starting point and irrespective of whether the objective technical problem is formulated as the provision of an alternative or an improved method of making a modified antibody having reduced core fucosylation.

Inventive step (Article 56 EPC) - claim 21

47. The opposition division did not decide on inventive step of claim 21 of the main request because it found this claim to contravene the requirements of Article 123(2) and (3) and Article 84 EPC. Auxiliary

request 5 upheld in the decision under appeal did not contain any product claim.

48. As regards inventive step of claim 21, the opponent merely referred to their reasoning "*presented in detail in the Grounds of Appeal, and over the documents discussed there in detail*" (item III.1 on page 10 of the opponent's reply to the proprietor's statement of grounds of appeal (see section VIII. above)). In the opponent's statement of grounds of appeal (items V.3.1, V.4 and V.5), inventive step of the claimed subject-matter was assessed using document D12 or D13 as the closest prior art. Hence, according to item III.1 of the opponent's reply, inventive step of the subject-matter of claim 21 should also be assessed using document D12 or D13 as the closest prior art.

49. However, in item III.2 of their reply, the opponent further stated that "*it was obvious to add a cell or cell line expressing antibodies to the cell culture medium to produce the antibodies*". This statement could imply that, rather than document D12 or D13, a document disclosing a culture medium comprising a fucose analogue should be used as the closest prior art for the assessment of inventive step of the subject-matter of claim 21. The opponent, however, neither further substantiated this line of attack nor indicated which documents should be used. Consequently, the board is not in a position to take this line of attack into account and therefore limits itself to the line of argument presented by the opponent in its statement of grounds of appeal.

50. Starting from the disclosure of document D12 or D13, the same considerations as for claim 1 (see points 35. to 46. above) apply to claim 21, which recites the same

fucose analogues as claim 1 (see section IV. above). In particular, since it was not obvious to the skilled person that antibodies having reduced core fucosylation could be made by culturing host cells expressing antibodies in the presence of a fucose analogue as recited in the claims (see point 45. above), the provision of a mammalian cell culture medium for the production of antibodies or antibody derivatives having reduced core fucosylation comprising a mammalian cell or cell line that expresses an antibody or antibody derivative and an effective amount of such a fucose analogue was not obvious to the skilled person, either.

51. The subject-matter of claim 21 therefore involves an inventive step for the same reasons as claim 1 (see points 35. to 46. above).

52. Consequently, the board holds that the claims of the main request meet the requirements of Article 56 EPC.

Sufficiency of disclosure (Article 83 EPC)

53. It is established case law of the boards that a successful objection of lack of sufficiency of disclosure presupposes that alleged serious doubts are substantiated by verifiable facts (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, II.C.5.3., II.C.7.1.4 and II.C.9.).

54. In the case at hand, the patent discloses that various different fucose analogues falling within the claimed range are able to reduce core fucosylation of antibodies when added to the cell culture medium of antibody-producing cells (Tables 1 and 2 of the patent). This has not been contested by the opponent.

55. However, the opponent argued that the patent did not enable the skilled person to obtain reduced core fucosylation of antibodies with all claimed analogues, i.e. the invention could not be performed over the whole claimed range.

56. In a first line of argument, the opponent considered that the patent itself showed that compounds falling within the claimed range (5-cyano fucose tetraacetate, fluoromethylene fucose or its peracetate and alkynyl fucose 1,2,3-tri(trimethylacetate)) were not able to inhibit core fucosylation.

57. However, this line of argument fails to convince the board. For the compound 5-cyano fucose tetraacetate, the patent discloses a measurable inhibition of core fucosylation of at least 5 to 10% (Table 1, page 39, lines 41 to 45), i.e. a reduction in core fucosylation when using this compound.

58. For fluoromethylene fucose or its peracetate, the opponent has not provided any evidence that indeed no inhibition of core fucosylation by this compound occurred. The mere fact that incorporation of fluoromethylene fucose was observed in more than 90% of the antibodies (Table 3 of the patent) is, in the board's view, not sufficient to raise serious doubts that they exhibit at least some inhibitory activity. Furthermore, the fact that the related fucose analogues chloro-, bromo- and iodo-fucose tetraacetate all have inhibitory activity (see Table 1 of the patent) seems to support the skilled person's expectation that fluoromethylene fucose and its peracetate would have at least some inhibitory activity.

The opponent further argued that document D14 confirmed that fluoromethylene fucose had no inhibitory effect on fucosylation of macromolecules. However, as pointed out above (see point 41.), the skilled person cannot draw any conclusions from the disclosure of document D14 with respect to a possible inhibition or reduction of protein fucosylation by any of the halogenated fucose analogues analysed in this document. The board hence considers that the opponent has not raised serious doubts substantiated by verifiable facts that the claimed invention could be carried out with the fucose analogues fluoromethylene fucose or its peracetate.

59. The compound alkynyl fucose 1,2,3-tri(trimethyl-acetate) showed, according to Table 1 of the patent, "*~0%*" inhibition at a concentration of 50 µM, whereas inhibition at 1 mM could not be detected (page 40, lines 41 to 44).

60. The proprietor argued that in view of the inhibitory activity shown in Table 1 for the related compounds alkynyl fucose tetrakis(trimethyl-acetate) and alkynyl fucose di(trimethyl-acetate) (Table 1, page 40, lines 31 to 39 and 45 to 48), the skilled person would have expected the data for alkynyl fucose 1,2,3-tri(trimethyl-acetate) in Table 1 to be erroneous. When reviewing the original data underlying Table 1 of the patent, the proprietor discovered that more than 80% inhibition had been achieved with this compound, i.e. that the data in Table 1 of the patent was indeed erroneous (document X5). The claimed method thus could be carried out for this compound.

61. The board notes that the opponent has not denied that the compound alkynyl fucose 1,2,3-tri(trimethyl-acetate) is able to reduce core fucosylation of

antibodies when used in a method according to claim 1 of the patent, i.e. that the claimed method could be carried out when using this compound. Rather, the opponent argued, with reference to decision G 2/93 of the Enlarged Board of Appeal (OJ EPO 1995, 275), that sufficiency of disclosure had to be judged on the basis of the information accessible to the skilled person at the filing date of the patent and taking into account the common general knowledge of the skilled person. Document X5 could therefore not be taken into account as it was not available to the skilled person at the filing date of the patent. The information presented to the skilled person at the filing date of the patent was that the claimed method could not be carried out when using alkynyl fucose 1, 2, 3-tri(trimethylacetate).

62. However, the board considers that based on the data disclosed in Table 1, the skilled person would not have concluded that the compound alkynyl fucose 1, 2, 3-tri(trimethylacetate) had no inhibitory activity at all under all circumstances. Firstly, the indication of an inhibition of approximately 0% ("*~0%*") does not have the same meaning as an indication of no inhibition, for which the number "*0*" is used in the patent (see Table 2 on page 41, lines 35, 39, 44 and 47). Furthermore, as evident from Tables 1 and 2, most compounds for which at the lower concentration either "*~0%*" or "*0*" inhibition was detected were able to inhibit core fucosylation at the higher concentration.

63. This information together with the information that the related compounds tetrakis(trimethyl-acetate) and alkynyl fucose di(trimethyl-acetate) had inhibitory activity conveyed to the skilled person that the compound alkynyl fucose 1, 2, 3-tri(trimethylacetate) would have some inhibitory activity when used at higher

concentrations. This is confirmed in the post-published data provided by the proprietor in document X5. The claimed invention thus can be carried out when using this compound.

64. Consequently, the board holds that the patent itself does not provide any information that would raise doubts that a reduction in core fucosylation could be achieved when employing any of the fucose analogues encompassed by the claims.

65. In a second line of argument, the opponent argued that the claims covered millions of compounds of which only a few were shown to be effective (Table 1). The skilled person would not expect compounds comprising large ester or ether groups in positions R^1 to R^4 to be functional since not all groups defined for R^1 to R^4 in the claims could be hydrolysed, as evident from documents D28 and D32.

66. However, the mere fact that a claim is broad is not in itself a ground for considering that a patent does not comply with the requirements of Article 83 EPC (see, for example, Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, II.C.7.1.4). In the case at hand, the opponent has not demonstrated that a specific compound with particular ether- or ester-groups at residues R^1 to R^4 had no activity and, in the board's opinion, documents D28 and D32 do not support the opponent's allegation that compounds comprising large ester or ether groups could not be functional.

67. Document D28 relates to the use of ethers for the protection of hydroxyl groups in organic synthesis reactions carried out under conditions not relevant for

reactions taking place within living cells and therefore does not contain any teaching relevant for the method of claim 1.

68. Document D32 (page 277) teaches that dealkylation of ethers in drug molecules is a "*common metabolic reaction*" and that "*usually*" only one ether is dealkylated in drug molecules comprising more than one ether group. However, this teaching instead supports the hypothesis put forward in paragraph [0058] of the patent that within the cells, metabolites or products of the fucose analogues comprising ethers may be produced.

69. Moreover, the patent discloses that a compound comprising an ether group at residue R^1 is active (1-methyl-2,3,4-triacetyl alkynyl fucose; see Table 1, page 41, line 5). Consequently, the opponent's second line of argument also fails to convince the board.

70. In a third line of argument, the opponent considered that since no clear structure-function relationship for the substitutions in position R^5 existed and minor structural changes at the R^5 position abolished the inhibitory activity of the compound, it was implausible that the multitude of claimed substituents in the R^5 position allowed for inhibition of core fucosylation. It was an undue burden for the skilled person to find out which of the millions of claimed compounds were effective.

71. However, this line of argument is based only on speculation since the opponent has not provided any evidence that particular substitutions in position R^5 falling within the claimed range would abolish the inhibitory activity of the compound.

72. Consequently, in view of the above considerations, the arguments and evidence brought forward by the opponent did not persuade the board that the patent does not sufficiently disclose the invention defined in the claims of the main request.

73. The board therefore concludes that the invention as defined in the claims of the main request meets the requirements of Article 83 EPC.

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 the patent with the following claims and a description to be adapted:
claims 1 to 26 of the main request filed with the statement of grounds of appeal.

The Registrar: The Chair:

I. Aperribay L. Bühler

Decision electronically authenticated