(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 December 2013 (05.12.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/181599 A3

(51) International Patent Classification:
C40B 30/04 (2006.01) *C12P 21/06* (2006.01)
C40B 20/08 (2006.01)

(21) International Application Number:
PCT/US2013/043710

(22) International Filing Date:
31 May 2013 (31.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/654,235 1 June 2012 (01.06.2012) US
61/784,697 14 March 2013 (14.03.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
12 March 2015

(54) Title: METHODS RELATED TO RITUXIMAB

Rituximab HC sequence (SEQ ID NO:1):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKF
KGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVASASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSSLGTQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
PGK

FIG. 1

(57) Abstract: The present invention relates to the characterization and production of rituximab.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/43710

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C40B 30/04; C40B 20/08; C12P 21/06 (2013.01)
USPC - 506/9; 506/6, 435/69.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 506/9; 506/6, 435/69.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 506/9, 6, 10, 18, 19; 435/69.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase; Google Patents, Scholar, Web; GenCore Sequence Search (AA)
Search terms: method of making biological therapeutic antibody,rituximab (Rituxan, MabThera), biosimilar, glycosylation profile or structure, complex carbohydrate G0F, fucose, C-terminal lysine, light chain or heavy chain pyroglutamate, BLA, 351(k) PHS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	FDA. Scientific Considerations in Demonstrating Biosimilariy to a Reference Product [online] February 2012 [retrieved 10 December 2013]. Available on the internet: <URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars">). Especially pg 1 para 2, pg 5 para 2, pg 6 para 2, pg 9 para 1-4.	1, 6, 8, 23-29 ---------- 7
Y ---- A	MA et al. Carbohydrate analysis of a chimeric recombinant monoclonal antibody by capillary electrophoresis with laser-induced fluorescence detection. Anal Chem 15 November 1999 Vol 71 No 22 Pages 5185-5192. Especially pg 5187 fig 1, pg 5191 col 1 para 4, pg 5191 Table 3.	1, 6, 8, 23-29 ---------- 7
Y ---- A	US 2005/0054832 A1 (LAZAR et al.) 10 March 2005 (10.03.2005). Especially para [0074], SEQ ID NOs: 3, 4	6, 8 ------ 7, 14
A	WO 2011/127322 A1 (COLLINS et al.) 13 October 2011 (13.10.2011). Especially para [0012], [0039], [0040], [0041], [0042].	14

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2013 (10.12.2013)	03 JAN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/43710

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☒ subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.4.1 SEQ ID NOs: 1, 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/43710

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 19, 21, 22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
----------continued on extra sheet----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-18 and 23-29 restricted to the first invention (Parameter #1, Complex G0F) (Claims 1, 6-8, 14, 23-29)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

continuation of Box III (Lack of Unity of Invention)

Group I+: Claims 1-18 and 23-29 drawn to a method of manufacturing rituximab drug product, comprising: providing or obtaining a test glycoprotein preparation; acquiring at least one value for an a rituximab listed in Table 1 for the test glycoprotein preparation; and processing at least a portion of the test glycoprotein preparation as rituximab drug product if the at least one value for the test glycoprotein preparation meets a reference criterion shown in Table 1 for the parameter, thereby manufacturing a rituximab drug product. The first invention is restricted to the first named Parameter in Table 1 (Parameter #1, Complex G0F). Group I+ will be searched to the extent that it reads on G0F, without fee. It is believed that claims 1, 6-8, 14, and 23-29 read on this first named invention. Applicants must indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be: the second named Parameter in Table 1, Parameter #2, Complex (claims 1-8, 14-18, and 23-29).

The inventions listed as Group I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features
The special technical features is the rituximab parameters recited in Table 1. The inventions do not share a special technical feature, because rituximab variants characterized by post-translational modifications (e.g., glycan structures and/or primary sequence modifications as defined in the parameters in Table 1), would have displayed different pharmacokinetic and therapeutic properties. Without a shared special technical feature, the inventions lack unity with one another.

Common Technical Features

The inventions of Groups I+ share the common technical feature of providing or obtaining a test glycoprotein preparation, acquiring at least one value for an antibody parameter listed in Table 1 for the test glycoprotein preparation; and processing at least a portion of the test glycoprotein preparation if the at least one value for the test glycoprotein preparation meets a reference criterion shown in Table 1 for the parameter, processing at least a portion of the test glycoprotein preparation as rituximab drug product if the at least one value for the test glycoprotein preparation meets a reference criterion shown in Table 1 for the parameter, thereby manufacturing rituximab drug product. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 2009/0311732 A1 to ROSSI et al. (hereinafter "Rossi"). Rossi discloses obtaining a test glycoprotein preparation (para [0076]; "The sample comprising the protein may for example correspond to a purified protein, e.g. when testing development lots, or to a pharmaceutical preparation, e.g. when carrying out lot release testing... para [0077]; In one embodiment of the invention, the protein according to the invention is an antibody"... para [0078]: "Preferably, said antibody is [...] rituximab"), processing at least a portion of the test glycoprotein preparation if the at least one value for the test glycoprotein preparation meets a reference criterion shown in Table 1 for the parameter [e.g. parameter 7, C-terminal lysine <25.00%] (para [0001]; "This invention provides analytical methods for quantification of truncation at the C-terminus of an Fc-containing protein such as e.g. antibodies and Fc-fusion proteins. More specifically, the methods of the present invention allow testing the proportion of said protein for which the C-terminal lysine has been cleaved off by an endoprotease present within the producer cell"; para [0121]-" In FIG. 2, the TACI-Fc sample comprises about 20% Lys1 variants and about 80% Lys0 variants"), processing at least a portion of the test glycoprotein preparation as rituximab drug product if the at least one value for the test glycoprotein preparation meets a reference criterion shown in Table 1 for the parameter (para [0076], [0078]), thereby manufacturing rituximab drug product (para [0076]; " e.g. when characterizing a protein in the frame of a marketing authorization submission or when carrying out lot release testing").

In addition, WO 2011/127325 A1 to COLLINS et al. (hereinafter 'Collins') teach a method for providing or obtaining a test glycoprotein preparation (pg 1, para 4 to pg 2, para 1, a biosimilar or biogeneric product that best matches the glycosylation properties of the host cell in which the marketed biologic therapeutic glycoprotein was produced; pg 44, Table 3, rituximab or Rituxan) acquiring at least one value for an antibody parameter for the test glycoprotein preparation (pg 47, para 1, Table 4, and Fig.1, Analysis of glycan structure); and processing at least a portion of the test glycoprotein preparation if the at least one value for the test glycoprotein preparation meets a reference criterion (pg 2, para 2, In one aspect, the invention features, a method of making a glycoprotein having a selected post-translational modification), processing at least a portion of the test glycoprotein preparation as rituximab drug product if the at least one value for the test glycoprotein preparation meets a reference criterion, thereby manufacturing rituximab drug product (pg 3, para 4, In one embodiment, the method is a method of making a glycoprotein having a selected post-translational modification (e.g., a selected glycostructure, glycan complement, glycan component, e.g., with a selected glycan structure) and, the method further comprises (b) making a glycoprotein having a selected post-translational modification (e.g., glycostructure, glycan complement, glycan component, e.g., with a selected glycan structure) in said selected cell population.).

As the common technical feature, rituximab post-translational modifications comprising various glycan structures and primary sequence modifications, was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Group I+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Comment on Item 4:
Claims 19, 21 and 22 are multiply dependent claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a).

Observations about certain claims:
For the purposes of the ISR, claim 11 is interpreted to depend on claim 10 rather than claim 8, as is written, because claim 11 will be a duplication of claim 7, if claim 11 is dependent on claim 8.

Claim 20 is absent.

Claim 24 is objected to because it depends from a subsequent claim, claim 28. For the purposes of the ISR, claim 24 is interpreted not to depend on claim 28.