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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2016 (09.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/141303 A3

(51) International Patent Classification:
*C12P 19/34* (2006.01) *C07K 16/28* (2006.01)
*A61K 39/395* (2006.01)

(21) International Application Number:
PCT/US2016/020920

(22) International Filing Date:
4 March 2016 (04.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/128,284 4 March 2015 (04.03.2015) 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, 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, SA, 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.

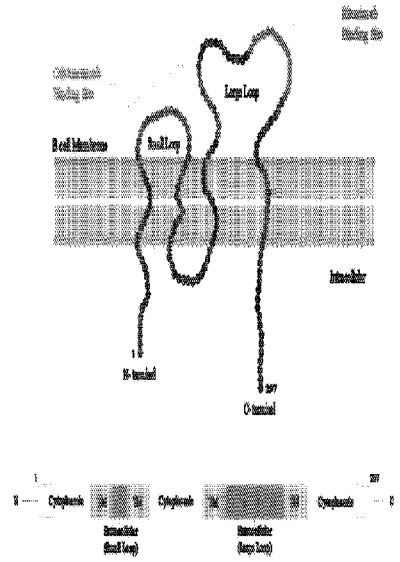
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

*[Continued on next page]*

(54) Title: CD20 BINDING MOLECULES AND USES THEREOF

(57) Abstract: This disclosure provides pentameric and hexameric CD20 binding molecules and methods of using such molecules to direct complement-mediated, T-cell-mediated, or both complement- mediated and T-cell-mediated killing of CD20-expressing cells.

Figure 1



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GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, 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**:
3 November 2016

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20920

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12P 19/34; A61K 39/395; C07K 16/28 (2016.01)
CPC - C07K 16/2887; C40B 30/04, 40/10; A61K 51/1027
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)
IPC(8) Classifications: C12P 19/34; A61K 39/395; C07K 16/28; CPC Classifications: C07K 16/2887; C40B 30/04, 40/10; A61K 51/1027

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO); USPTO Web Page; Google; Google Scholar; EBSCO; Entrez Pubmed; Science Direct; Search terms -- multimer, multivalent, antibody, IgA, IgM, 'heavy chain constant region', anti-CD20, complement, Calpha1, Calpha2, Cmu3, Cmu4-tp, IgG1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>–<br>Y | US 2010/0184959 A1 (GULER-GANE, G et al.) July 22, 2010; abstract; paragraph [0020], [0045], [0067], [0068], [0093], [0097], [0133], [0134]; SEQ ID NOs: 26, 28 | 1-2<br>------<br>3/1-2, 4/1-2, 5/3/1-2, 6/5/3/1-2, 10/1-2 |
| Y | US 2010/0279939 A1 (LEDBETTER, JA et al.) November 04, 2010; paragraphs [0053]-[0055], [0159], [0168], [0389], [0395], [0509], [0000], [0714], [0704] | 3/1-2, 4/1-2, 5/3/1-2, 6/5/3/1-2, 80, 83-84 |
| Y | US 2010/0093979 A1 (LANZA, GA) April 15, 2010; paragraphs [0047], [0119] | 5/3/1-2, 6/5/3/1-2, 83-84 |
| Y | US 2005/0003431 A1 (WUCHERPFENNIG, KW et al.) January 06, 2005; paragraphs [0041], [0042], [0082], [0190]; figures 2, 3 | 10/1-2 |
| Y | US 2009/0130089 A9 (SMITH, ES et al.) May 21, 2009; abstract; paragraphs [0008], [0009], [0081], [0104], [0106] | 80, 83-84 |
| A | US 6,476,198 B1 (KANG, AS) November 05, 2002; entire document | 1-2, 3/1-2, 4/1-2, 5/3/1-2, 6/5/3/1-2, 10/1-2, 11/10/1-2, 80, 83-84, 87-88 |
| P, X | WO 2015/053887 A1 (IGM BIOSCIENCES, INC.) April 16, 2015 | 1-2, 3/1-2, 4/1-2, 5/3/1-2, 6/5/3/1-2, 10/1-2, 11/10/1-2, 80, 83-84, 87-88 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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 |
|---|---|
| 11 August 2016 (11.08.2016) | 31 AUG 2016 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20920

**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:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

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 forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20920

**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.: 7-9, 12-79, 85-86, 89-112
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 Within the Next Supplemental Box-***-

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.:
1-6, 10-11, 80, 83-84, 87-88; restricted to SEQ ID NOs: 38-45

**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.

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-6, 10, 11, 80-84, 87, 88 and SEQ ID NOs: 38-45 are directed toward a multimeric binding molecule comprising at least two bivalent binding units, or variants or fragments thereof, wherein each binding unit comprises at least two heavy chain constant regions or fragments thereof, each associated with an antigen-binding domain, wherein at least one antigen binding domain of the binding molecule is a CD20 antigen binding domain; and a method for directing complement-mediated or T-cell-mediated killing of a CD20-expressing cell therewith.

The multimeric binding molecule and method will be searched to the extent that the binding molecule comprises a VH encompassing SEQ ID NO: 38 (first exemplary VH), comprising a CDR1 encompassing SEQ ID NO: 39 (first exemplary HCDR1), a CDR2 encompassing SEQ ID NO: 40 (first exemplary HCDR2) and a CDR3 encompassing SEQ ID NO: 41 (first exemplary HCDR3); and a VL encompassing SEQ ID NO: 42 (first exemplary VL) comprising a CDR1 encompassing SEQ ID NO: 43 (first exemplary LCDR1), a CDR2 encompassing SEQ ID NO: 44 (first exemplary LCDR2) and a CDR3 encompassing SEQ ID NO: 45 (first exemplary LCDR3). Applicant is invited to elect additional pair(s) of VH and VL sequence(s), optionally with specified CDRs of said VH and VL sequence(s), with specified SEQ ID NO: for each CDR or specified substitution(s) at specified site(s) of a SEQ ID NO: for a CDR, to be searched. Additional pair(s) of VH and VL sequence(s) and/or associated CDR sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-6, 10, 11, 80, 83 (in-part), 84 (in-part), 87 (in-part) and 88 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 38 (VH), SEQ ID NO: 39 (HCDR1), SEQ ID NO: 40 (HCDR2), SEQ ID NO: 41 (HCDR3), SEQ ID NO: 42 (VL), SEQ ID NO: 43 (LCDR1), SEQ ID NO: 44 (LCDR2) and SEQ ID NO: 45 (LCDR3). Applicants must specify the claims that encompass any additionally elected VH and/or VL and/or associated CDR sequence(s). Applicants must further indicate, if applicable, the claims which encompass 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 a VH encompassing SEQ ID NO: 1 (first exemplary elected VH), comprising a CDR1 encompassing SEQ ID NO: 2 (first exemplary elected HCDR1), a CDR2 encompassing SEQ ID NO: 3 (first exemplary elected HCDR2) and a CDR3 encompassing SEQ ID NO: 4 (first exemplary elected HCDR3); and a VL encompassing SEQ ID NO: 5 (first exemplary elected VL) comprising a CDR1 encompassing SEQ ID NO: 6 (first exemplary elected LCDR1), a CDR2 encompassing SEQ ID NO: 7 (first exemplary elected LCDR2) and a CDR3 encompassing SEQ ID NO: 8 (first exemplary elected LCDR3).

No technical features are shared between the heavy chain sequences of Groups I+ and/or the light chain sequences of Groups I+, and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a multimeric binding molecule comprising at least two bivalent binding units, or variants or fragments thereof, wherein each binding unit comprises at least two heavy chain constant regions or fragments thereof, each associated with an antigen-binding domain, wherein at least one antigen binding domain of the binding molecule is a CD20 antigen binding domain comprising six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 39 or SEQ ID NO: 39 with one or two single amino acid substitutions; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 40 with one or two single amino acid substitutions; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 41, SEQ ID NO: 41 with one or two single amino acid substitutions; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 43, or SEQ ID NO: 43 with one or two single amino acid substitutions; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 44 or SEQ ID NO: 44 with one or two single amino acid substitutions; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 45 or SEQ ID NO: 45 with one or two single amino acid substitutions; wherein at least one antigen binding domain of the binding molecule comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL), wherein the VH comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 38, and the VL comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 42; and a method for directing complement-mediated, T-cell-mediated, or both complement-mediated and T-cell-mediated killing of a CD20-expressing cell comprising contacting a CD20-expressing cell with a dimeric, pentameric, or hexameric binding molecule comprising two, five, or six bivalent binding units, respectively, wherein each binding unit comprises two IgA or IgM heavy chain constant regions or fragments thereof and two antigen binding domains, wherein at least one antigen binding domain of the binding molecule is a CD20 antigen binding domain, and wherein the binding molecule can direct complement-mediated killing of a CD20-expressing cell at higher potency than an equivalent amount of a monospecific, bivalent IgG1 antibody or fragment thereof that specifically binds to the same CD20 epitope as the CD20 antigen binding domain.

However, these shared technical features are previously disclosed by US 6,476,198 B1 (KANG) in view of US 2010/0184959 A1 to Guler-Gane et al. (hereinafter 'Guler-Gane').

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

Kang discloses a multimeric binding molecule (a multimeric antigen-binding molecule; column 3, line 54-column 4, line 1) comprising at least two bivalent binding units (comprising four monovalent polypeptides (comprising at least two bivalent binding units); column 14, lines 28-38), wherein each binding unit comprises at least two constant regions or fragments thereof (wherein each binding unit comprises at least two constant regions or fragments thereof; column 14, lines 28-38), each associated with an antigen-binding domain (each associated with an antigen-binding domain; column 13, lines 22-27; column 14, lines 28-38), wherein at least one antigen binding domain of the binding molecule comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) (wherein at least one antigen binding domain of the binding molecule comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL)); column 13, lines 28-40); and a method for directing complement-mediated, T-cell-mediated, killing of an antigen-expressing cell (a method for activating T cells and providing antibody-mediated cytotoxicity (a method for directing complement-mediated, T-cell-mediated, killing of an antigen-expressing cell); column 13, lines 41-52; column 34, lines 30-36) comprising contacting an antigen-expressing cell (comprising contacting an antigen-expressing cell; column 13, lines 41-52; column 34, lines 30-36) with a dimeric binding molecule comprising two bivalent binding units (with a dimeric binding molecule comprising two bivalent binding units; column 14, lines 28-38; column 34, lines 30-36), wherein each binding unit comprises IgA or IgM heavy chain constant regions or fragments thereof (wherein each binding unit comprises IgA or IgM heavy chain constant regions or fragments thereof; column 17, lines 10-16) and two antigen binding domains (and two antigen binding domains; column 14, lines 28-38), wherein the binding molecule can direct complement-mediated killing of an antigen-expressing cell (wherein the binding molecule can direct complement-mediated killing of an antigen-expressing cell; column 13, lines 41-52; column 34, lines 30-36) at higher potency than an equivalent amount of a monospecific, bivalent IgG1 antibody or fragment thereof that specifically binds to the same epitope as the antigen binding domain (wherein the multimeric antibodies exhibit greater avidity over the same monomeric antigen binding proteins (at higher potency than an equivalent amount of a monospecific, bivalent IgG1 antibody or fragment thereof that specifically binds to the same epitope as the antigen binding domain); column 3, line 58 - column 4, line 4).

Kang does not disclose wherein each binding unit comprises at least two IgA or IgM heavy chain constant regions or fragments thereof; wherein at least one antigen binding domain of the binding molecule is a CD20 antigen binding domain comprising six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 39 or SEQ ID NO: 39 with one or two single amino acid substitutions; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 40 with one or two single amino acid substitutions; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 41, SEQ ID NO: 41 with one or two single amino acid substitutions; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 43, or SEQ ID NO: 43 with one or two single amino acid substitutions; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 44 or SEQ ID NO: 44 with one or two single amino acid substitutions; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 45 or SEQ ID NO: 45 with one or two single amino acid substitutions; wherein the VH comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 38, and the VL comprises an amino acid sequence at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to SEQ ID NO: 42; a CD20-expressing cell; and wherein at least one antigen binding domain of the binding molecule is a CD20 antigen binding domain, and wherein the binding molecule can direct complement-mediated killing of a CD20-expressing cell at higher potency than an equivalent amount of a monospecific, bivalent IgG1 antibody or fragment thereof that specifically binds to the same CD20 epitope as the CD20 antigen binding domain.

Guler-Gane discloses multispecific, and multivalent antibodies (multispecific and multivalent antibodies; paragraphs [0090], [0093]), including a bivalent fragment comprising two linked Fab fragments (including a bivalent fragment comprising two linked Fab fragments; paragraph [0093]), wherein each Fab fragment comprises a CH domain (wherein each Fab fragment comprises a CH domain; paragraph [0093]) wherein the CH1 domain comprises modifications that alter effector function (wherein the CH1 domain comprises modifications that alter effector function; paragraph [0097]); and wherein the antigen binding domain binds to CD20 (wherein the antigen binding domain binds to CD20; paragraphs [0133], [0134]) and comprises six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 (and comprises VH and VL CDR sequences (and comprises six immunoglobulin complementarity determining regions HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3); paragraph [0082], [0133], [0134]), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 39 (wherein the heavy chain comprises the HCRDR1 sequence GYSFTSYWIG (wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 39); paragraph [0134], SEQ ID NO: 26, residues 26-35 are 100% identical to Applicants' SEQ ID NO: 39); the HCDR2 comprises the amino acid sequence of SEQ ID NO: 40 (wherein the HCDR2 comprises the amino acid sequence IIYPGDSDTRYSPSFQG (the HCDR2 comprises the amino acid sequence of SEQ ID NO: 40); paragraph [0134], SEQ ID NO: 26, residues 50-66 are 100% identical to Applicants' SEQ ID NO: 40); the HCDR3 comprises the amino acid sequence of SEQ ID NO: 41 (the HCDR3 comprises the amino acid sequence HPSYGSGSPNFDY (the HCDR3 comprises the amino acid sequence of SEQ ID NO: 41); paragraph [0134], SEQ ID NO: 26, residues 99-111 are 100% identical to Applicants' SEQ ID NO: 41); the LCDR1 comprises the amino acid sequence of SEQ ID NO: 43 (the LCDR1 comprises the amino acid sequence RSSQSLVYSDGNTYLS (the LCDR1 comprises the amino acid sequence of SEQ ID NO: 43); paragraph [0134], SEQ ID NO: 28, residues 24-39 are 100% identical to Applicants' SEQ ID NO: 43); the LCDR2 comprises the amino acid sequence of SEQ ID NO: 44 (the LCDR2 comprises the amino acid sequence KISNRFS (he LCDR2 comprises the amino acid sequence of SEQ ID NO: 44); paragraph [0134], SEQ ID NO: 28, residues 55-61 are 100% identical to Applicants' SEQ ID NO: 44); and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 45 (the LCDR3 comprises the amino acid sequence VQATQFPLT (the LCDR3 comprises the amino acid sequence of SEQ ID NO: 45); paragraph [0134], SEQ ID NO: 28, residues 94-102 are 100% identical to Applicants' SEQ ID NO: 45); wherein the VH comprises an amino acid sequence 100% identical to SEQ ID NO: 38 (wherein the VH comprises SEQ ID NO: 26 (wherein the VH comprises an amino acid sequence 100% identical to SEQ ID NO: 38); paragraph [0134], SEQ ID NO: 26, wherein SEQ ID NO: 26 is 100% identical to Applicants' SEQ ID NO: 38), and the VL comprises an amino acid sequence 100% identical to SEQ ID NO: 42 (and the VL comprises SEQ ID NO: 28 (the VL comprises an amino acid sequence 100% identical to SEQ ID NO: 42); paragraph [0134], SEQ ID NO: 28, wherein SEQ ID NO: 28 is 100% identical to Applicants' SEQ ID NO: 42).

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Kang to have included the use of constructs, such as the bivalent Fab construct of Guler-Gane, comprising two CH domains per unit, in a multivalent construct comprising at least two such constructs, as disclosed by Kang, in order to better enable tailoring of the effector functions by using modified CH domains, as disclosed by Guler-Gane; and wherein the construct included the CD20-binding variable domains disclosed by Guler-Gane, in order to enable the binding and killing of a CD20-expressing cell, such as a cancer cell.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Kang and Guler-Gane references, unity of invention is lacking.