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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 November 2017 (09.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/193032 A3

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/46* (2006.01)
C07K 16/28 (2006.01) *C07K 16/18* (2006.01)

(21) International Application Number:
PCT/US2017/031356

(22) International Filing Date:
05 May 2017 (05.05.2017)

(25) Filing Language: English

(26) Publication Language: English

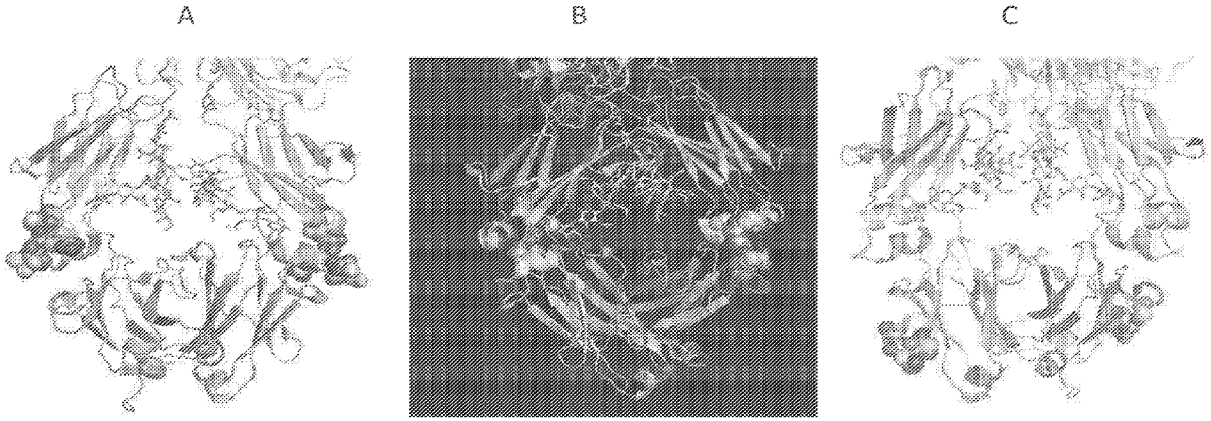
(30) Priority Data:
62/332,788 06 May 2016 (06.05.2016) US

(71) Applicant: **MEDIMMUNE, LLC** [US/US]; One MedImmune Way, Gaithersburg, MD 20878 (US).

(72) Inventors: **KASTURIRANGAN, Srinath**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **GAO, Changshou**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **RAINEY, Godfrey**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **MORROW, Michelle**; c/o MedImmune Limited, Milstein Building, Granta Park, Cambridge CB21 6GH (GB). **DOBSON, Claire, Louise**; c/o MedImmune Limited, Milstein Building, Granta Park, Cambridge CB21 6GH (GB). **DRABIC, Stacey**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **SCHOFIELD, Darren**; c/o MedImmune Limited, Milstein Building, Granta Park, Cambridge CB21 6GH (GB). **CARLESSO, Gianluca**; c/o MedImmune Limited, Milstein Building, Granta Park, Cambridge CB21 6GH (GB). **POLLIZZI, Kristen**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **MAZOR, Yariv**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **OBERST, Michael**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **HAMMOND, Scott, A.**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **LOBO, Brian**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **MANIKWAR, Prakash**; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US). **SEAMAN, Jonathan**; c/o MedImmune Limited, Milstein Building, Granta Park, Cambridge CB21 6GH (GB).

(54) Title: BISPECIFIC BINDING PROTEINS AND USES THEREOF

FIGURE 1



(57) Abstract: The disclosure generally provides proteins that bind two epitopes (e.g., a first and a second epitope) and that are bivalent for binding to each of the first and second epitopes. The disclosure also provides for specific binding proteins, including antibodies, which bind to a target protein. The disclosure also provides compositions comprising such proteins, nucleic acid molecules encoding such proteins and methods of making such proteins. The disclosure provides methods of inducing an immune response in a subject as well as methods for treating or preventing cancer in a subject by administering the proteins, nucleic acid molecules and/or compositions to the subject.

WO 2017/193032 A3

[Continued on next page]

(74) **Agent: MENSAH, Kwame, N.** et al.; c/o MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878 (US).

(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, DJ, 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, KH, KN, KP, KR, KW, 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, 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))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) **Date of publication of the international search report:**
14 December 2017 (14.12.2017)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/31356

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 39/395; C07K 16/28, 16/46, 16/18 (2017.01)
CPC - A61K 39/395, 39/39533; C07K 16/28, 16/18, 16/468, 16/46, 16/30

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/070565 A1 (MEDIMMUNE, LLC) May 16, 2013; abstract; paragraphs [0004], [0007]-[0009], [0021], [0072], [0077], [0128], [0133], [0256]-[0258]; figures 1, 2c	1-5, 7, 9/1-5, 9/7, 10/1-5, 10/7, 11/1-5, 11/7, 12/11/1-5, 12/11/7, 13/1-5, 13/7, 14/13/1-5, 14/13/7, 15/13/1-5, 15/13/7, 16/13/1-5, 16/13/7, 17/13/1-5, 17/13/7, 18/1-5, 18/7, 19/1-5, 19/7, 20/1-5, 20/7, 21/1-5, 21/7
Y	US 2015/0352225 A1 (REDWOOD BIOSCIENCES, INC.) December 10, 2015; paragraphs [0005], [0039], [0216], [0219], [0223], [0407], [0458], [0468], [0569], [0582]; figure 17B	1-5, 7, 9/1-5, 9/7, 10/1-5, 10/7, 11/1-5, 11/7, 12/11/1-5, 12/11/7, 13/1-5, 13/7, 14/13/1-5, 14/13/7, 15/13/1-5, 15/13/7, 16/13/1-5, 16/13/7, 17/13/1-5, 17/13/7, 18/1-5, 18/7, 19/1-5, 19/7, 20/1-5, 20/7, 21/1-5, 21/7
Y	US 2015/0274844 A1 (EMERGENT PRODUCT DEVELOPMENT SEATTLE LLC) October 1, 2015; paragraphs [0048], [0097].	12/11/1-5, 12/11/7

☒ 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
28 September 2017 (28.09.2017)	20 OCT 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/31356

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLOMA, MJ et al. Design And Production Of Novel Tetravalent Bispecific Antibodies. Nature Biotechnology. February 1997, Vol. 15, pages 159-163, DOI: 10.1038/nbt0297-159; abstract; page 159, first column, second paragraph- second column, first paragraph.	23-25, 26/23-25, 27/26/23-25, 30/23-25, 31/23-25
A	US 2014/0243504 A1 (REGENERON PHARMACEUTICALS, INC.) August 28, 2014; abstract; paragraphs [0014], [0018].	23-25, 26/23-25, 27/26/23-25, 30/23-25, 31/23-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/31356

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.: 22, 28, 29, 32-35, 52-58
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:
-***-Please See Supplemental Page-***-

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.:
1-5, 7, 9-21, 23-27, 30, 31; SEQ ID NO: 39

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/31356

-***-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 1-21, 23-27, 30, 31 and ISTRP (SEQ ID NO: 39) are directed toward a tetravalent bispecific binding protein comprising a first binding domain (BD1) that binds to a first epitope, a second binding domain (BD2) that binds to a second epitope, and an Fc region comprising CH2 and CH3 domains; wherein the Fc region comprises BD2 at a solvent exposed loop in the CH2 domain, the CH3 domain, or at the interface of the CH2 and CH3 domains.

The protein will be searched to the extent that it encompasses a loop encompassing ISRTP (SEQ ID NO: 39) (first exemplary loop sequence). Applicant is invited to elect additional loop sequence(s), either as fully specified loop sequence(s), or with a specified SEQ ID NO: for each elected loop sequence, to be searched. Additional loop sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-5, 7, 9 (in-part), 10 (in-part), 11 (in-part), 12 (in-part), 13 (in-part), 14 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 18 (in-part), 19 (in-part), 20 (in-part), 21 (in-part) 23-27, 30 and 31 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass ISRTP (SEQ ID NO: 39) (loop sequence). Applicants must specify the claims that encompass any additionally elected loop 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 loop sequence encompassing "SNG" (first exemplary elected loop sequence).

Groups II+, Claims 36-39, 43-45, and SEQ ID NOs: 1 and 2 are directed toward a bispecific binding protein that binds to PD-1 and a second target, wherein the second target is either CTLA-4 or TIM3.

The bispecific binding protein(s) can be searched to the extent that they comprise a first peptide encompassing SEQ ID NO: 1 (first exemplary polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 2 (second exemplary polypeptide sequence). Applicant is invited to elect additional binding protein(s), with specified SEQ ID NO(s): associated therewith, to be searched. Additional binding protein sequence(s) can be searched upon the payment of additional fees. It is believed that claim 36 encompasses this first named invention of Groups (II)+ and thus this claims can be searched with payment of a fee for the search of Groups (II)+, to the extent that it encompasses sequence SEQ ID NO: 1 (polypeptide sequence) and SEQ ID NO: 2 (polypeptide sequence). Applicants must specify the claims that encompass any additionally elected binding protein(s) and associated sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups (II)+, 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) can result in only the first claimed invention of groups (II)+ to be searched/examined. An exemplary election would be a binding protein encompassing a first polypeptide encompassing SEQ ID NO: 5 (first exemplary elected polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 6 (second exemplary elected polypeptide sequence).

Groups III+, Claims 40-42 and SEQ ID NOs: 14 and 15 are directed toward a bispecific binding protein that binds to PD-L1 and CTLA-4.

The bispecific binding protein(s) can be searched to the extent that they comprise a first peptide encompassing SEQ ID NO: 14 (first exemplary polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 15 (second exemplary polypeptide sequence). Applicant is invited to elect additional binding protein(s), with specified SEQ ID NO(s): associated therewith, to be searched. Additional binding protein sequence(s) can be searched upon the payment of additional fees. It is believed that claim 40 encompasses this first named invention of Groups (III)+ and thus this claims can be searched with payment of a fee for the search of Groups (III)+, to the extent that it encompasses sequence SEQ ID NO: 14 (polypeptide sequence) and SEQ ID NO: 15 (polypeptide sequence). Applicants must specify the claims that encompass any additionally elected binding protein(s) and associated sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups (III)+, 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) can result in only the first claimed invention of groups (III)+ to be searched/examined. An exemplary election would be a binding protein encompassing a first polypeptide encompassing SEQ ID NO: 16 (first exemplary elected polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 17 (second exemplary elected polypeptide sequence).

The bispecific binding protein(s) can be searched to the extent that they comprise a first peptide encompassing SEQ ID NO: 34 (first exemplary polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 32 (second exemplary polypeptide sequence). Applicant is invited to elect additional binding protein(s), with specified SEQ ID NO(s): associated therewith, to be searched. Additional binding protein sequence(s) can be searched upon the payment of additional fees. It is believed that claim 46 encompasses this first named invention of Groups (IV)+ and thus this claims can be searched with payment of a fee for the search of Groups (IV)+, to the extent that it encompasses sequence SEQ ID NO: 34 (polypeptide sequence) and SEQ ID NO: 32 (polypeptide sequence). Applicants must specify the claims that encompass any additionally elected binding protein(s) and associated sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups (IV)+, 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) can result in only the first claimed invention of groups (IV)+ to be searched/examined. An exemplary election would be a binding protein encompassing a first polypeptide encompassing SEQ ID NO: 36 (first exemplary elected polypeptide sequence), and a second polypeptide encompassing SEQ ID NO: 93 (second exemplary elected polypeptide sequence).

Group V, Claims 49-51 are directed toward an antibody or antigen binding fragment thereof that binds to TIM3.

The inventions listed as Groups I+ through IV+ and V 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: the special technical features of Groups I+ include wherein the Fc region comprises BD2 at a solvent exposed loop in the CH2 domain, the CH3 domain, or at the interface of the CH2 and CH3 domains, not present in any other Groups; the special technical features of Groups II+ include SEQ ID NO: 1, not present in any other Groups; the special technical features of Groups III+ include SEQ ID NO: 14, not present in any other Groups; the special technical features of Groups IV+ include SEQ ID NO: 32, not present in any other Groups; the special technical features of Group V include SEQ ID NO: 79, not present in any other Groups.

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

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

Groups I+ through IV+ and V share the technical features including: binding proteins. Groups I+ through IV+ share the technical features including: bispecific binding proteins, comprising at least a first peptide and a second peptide. Groups II+ and III+ share the technical features including: binding to CTLA4. Groups II+ and V share the technical features including: binding to TIM3. Groups III+ and IV+ share the technical features including: binding to PD-L1. Groups I+ share the technical features including: a protein, comprising: a first binding domain (BD1) that binds to a first epitope, a second binding domain (BD2) that binds to a second epitope, and an Fc region comprising CH2 and CH3 domains; wherein the Fc region comprises BD2 at a solvent exposed loop in the CH2 domain, the CH3 domain, or at the interface of the CH2 and CH3 domains; and wherein the protein is bivalent for binding to each of the first and second epitopes. Groups II+ share the technical features including: a bispecific binding protein that binds to PD-1 and CTLA4; and a bispecific binding protein that binds to PD-1 and TIM3. Groups III+ share the technical features including: a bispecific binding protein that binds to PD-L1 and CTLA4. Groups IV+ share the technical features including: a bispecific binding protein that binds to OX40 and PD-L1 and SEQ ID NO: 32.

However, these shared technical features are previously disclosed by WO 2016/061142 A1 to Novartis AG et al. (hereinafter 'Novartis') in view of the article 'Design and production of novel tetravelant bispecific antibodies' by Coloma et al. (hereinafter 'Coloma'), as evidenced by the article 'Introducing antigen-binding sites in structural loops of immunoglobulin constant domains: Fc fragments with engineered HER2/neu-binding sites and antibody properties' by Wozniak-Knopp et al. (hereinafter 'Wozniak') and further in view of WO 2016/057667 A1 to MedImmune LLC (hereinafter 'MedImmune').

Novartis discloses bispecific binding proteins (bispecific antibody molecules (binding proteins); page 3, lines 22-29), comprising at least a first peptide and a second peptide (comprising a first and a second antibody molecule or fragment thereof (a first peptide and a second peptide); page 43, lines 5-10); binding to CTLA4 (an anti-CTLA4 antibody (binding to CTLA4); page 39, line 1; page 43, lines 7-16); binding to TIM3 (binding to Tim-3; page 17, lines 13-20; page 43, lines 7-10); binding to PD-L1 (binding to PD-L1; page 17, lines 13-20; page 43, lines 7-10); a protein, comprising: a first binding domain (BD1) that binds to a first epitope (a bispecific antibody comprising a first antibody molecule (domain (BD1)) that binds to a first target (epitope); page 17, lines 15-20), a second binding domain (BD2) that binds to a second epitope (a second antibody molecule (binding domain (BD2)) that binds to a second target (epitope); page 17, lines 15-20), and an Fc region comprising CH2 and CH3 domains (and a full constant region (an Fc region comprising CH2 and CH3 domains); page 77, lines 10-13; page 89, lines 13-16); and wherein the protein is bivalent for binding to each of the first and second epitopes (wherein the bispecific antibody is tetravalent (bivalent for binding to each of the first and second epitopes); page page 17, lines 15-20; page 89, lines 27-31); a bispecific binding protein that binds to PD-1 and TIM3 (a bispecific binding protein that binds to PD-1 and TIM3; page 129, lines 25-30). Novartis further discloses administration of combinations of immunomodulators, including an anti-PD-1 or PD-L1 antibody with an inhibitor of CTLA4 (administration of combinations of immunomodulators, including an anti-PD-1 or PD-L1 antibody with an inhibitor of CTLA4; page 129, lines 9-16), and/or OX40 (and/or OX40; page 121, lines 24-31).

Novartis does not disclose wherein the Fc region comprises BD2 at a solvent exposed loop in the CH3 domain; and a bispecific binding protein that binds to PD-1 and CTLA4; a bispecific binding protein that binds to PD-L1 and CTLA4; a bispecific binding protein that binds to OX40 and PD-L1 and SEQ ID NO: 32.

Coloma discloses the production of tetravalent bispecific antibodies (the production of tetravalent bispecific antibodies; abstract) by fusing an scFv at a solvent exposed loop in the CH3 domain (by fusing an scFv at the C-terminus of the CH3 domain (at a solvent exposed loop in the CH3 domain); abstract, wherein, according to Wozniak, the tip of the C-terminus of the CH3 domain comprises loop structures (abstract, Fig. 1, Fig 2)).

MedImmune discloses a binding protein that binds to OX40 (anti-OX40 antibodies (a binding protein that binds to OX40); abstract), comprising SEQ ID NO: 32 (comprising SEQ ID NO: 30 (SEQ ID NO: 32); paragraph [0006]; wherein SEQ ID NO: 30 is 100% identical to Applicants' SEQ ID NO: 32).

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 Novartis to have provided combinations of immunomodulators, particularly antibodies, as part of bivalent or multivalent proteins including antibodies that bind to PD-1 or PD-L1, as disclosed by Novartis, with additional antibodies to CTLA4 and/or OX40, as disclosed by Novartis, in order to provide more effective targeting of the combined antibodies to single cells or cells in very close proximity. It further 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 Novartis to have specifically provided bispecific tetravalent structures, as disclosed by Coloma, by joining a second binding domain or molecule to a first molecule at an exposed loop at the tip of the CH3 domain, as disclosed by Coloma, in order to better enable the fusion of the binding molecules with minimal potential for interference of the binding domains with each other. It additionally 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 Novartis to have provided an anti-OX40 antibody comprising SEQ ID NO: 32, as disclosed by MedImmune, in order to enable the effective inhibition of OX40 using an antibody molecule or fragment thereof which would have been potentially combinable or fusable into a bispecific antibody, based on the disclosure of Novartis.

Since none of the special technical features of the Groups I+ through IV+ and V 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 Novartis, Coloma, and MedImmune references, unity of invention is lacking.