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(54) Title: TUMOR TARGETING CONJUGATES AND METHODS OF USE THEREOF

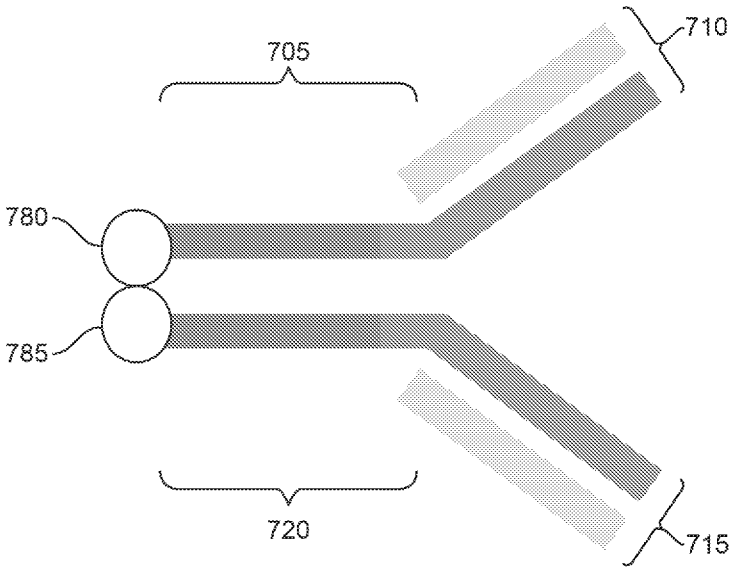

FIG. 1

(57) Abstract: Various compositions are disclosed. The compositions of conjugates comprising immune-stimulatory compounds are also provided. Additionally provided are the methods of preparation and use of the conjugates. This includes methods for treating disorders, such as cancer.

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[Continued on next page]

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).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/15607

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28, C07K 16/30, C07K 19/00 (2018.01)
CPC - A61K 47/48384, A61K 47/484, A61K 47/48415

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.
X ------ Y	US 2014/0154252 A1 (EMERGENT PRODUCT DEVELOPMENT SEATTLE, LLC) 05 June 2014 (05.06.2014) para [0054]-[0056]; [0108]; [0160]-[0162]; [0198]; [0315]-[0317].	2, 3 ------ 1, 4, 5, 60
Y	US 2013/0129729 A1 (KISCHEL et al.) 23 May 2013 (23.05.2013) para [0020]-[0022]; [0123]-[0125].	1, 4, 5, 60

☐ 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
16 July 2018	30 JUL 2018
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
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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/US 18/15607

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.: 6-59, 61-67, 75-99, 108-130
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:
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.

Group I, claims 1-5 and 60, directed to a recombinant bispecific antibody, and a method of making the same.

Group II, claims 68-74 and 100-107, directed to a conjugate comprising one or two antibody binding domains.

The inventions listed as Groups I-II do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

--continued on next 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.:
1-5, 60

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 III: Observations where unity of invention is lacking--

Special technical features:

Group I has the special technical feature of wherein the recombinant bispecific antibody induces greater immune cell activation when the recombinant bispecific antibody is bound to the tumor associated antigen and to the antigen on the antigen presenting cell as compared to when the recombinant bispecific antibody is bound to the antigen on the antigen presenting cell but not to the tumor associated antigen, that is not required by Group II.

Group II has the special technical feature of wherein a Kd for binding of the Fc domain to an Fc receptor in a presence of the first binding domain and the second binding domain is no greater than about 100 times a Kd for binding of the Fc domain to the Fc receptor in an absence of the second binding domain, and/or wherein a molar ratio of immune-stimulatory compound to antibody construct is less than 8, that is not required by Group I.

Common technical features:

Groups I-II share the common technical feature of a milti-specific recombinant protein construct, comprising a target antigen binding domain, wherein the target antigen binding domain specifically binds to a tumor associated antigen; an effector antigen binding domain, wherein the effector antigen binding domain specifically binds to an antigen on an antigen presenting cell and is an antibody antigen binding domain, wherein the antigen is a molecule on the antigen presenting cell; and a domain comprising an Fc region; an immune-stimulatory compound attached to the recombinant bispecific antibody by a linker; wherein the recombinant bispecific antibody induces immune cell activation when the recombinant antibody construct is bound to the tumor associated antigen and/or to the antigen on the antigen presenting cell. However, this shared technical feature does not represent a contribution over prior art, because this shared technical feature is made obvious by US 2014/0154252 A1 to Emergent Product Development Seattle, LLC. (hereinafter Emergent), in view of US 2013/0129729 A1 to Kischel et al., (hereinafter Kischel).

Emergent teaches a multi-specific recombinant antibody construct, comprising a target antigen binding domain, wherein the target antigen binding domain specifically binds to a tumor associated antigen; an effector antigen binding domain, wherein the effector antigen binding domain specifically binds to an antigen on an antigen presenting cell and is an antibody antigen binding domain, wherein the antigen is a molecule on the antigen presenting cell (para [0056]-[0057] "proteins in which the first and second binding domains are derived from the same, or different immunoglobulins (e.g., antibodies), and wherein the first and second binding domains recognize the same, or different, molecular targets (e.g., cell surface markers, such as membrane-bound proteins). For binding domains composed of at least two regions...a protein of the invention is a multivalent (e.g., multispecific) binding protein with effector function wherein at least one of the first binding domain and the second binding domain recognizes a target selected from the group consisting of a tumor antigen, a B-cell target, a TNF receptor superfamily member, a Hedgehog family member, a receptor tyrosine kinase, a proteoglycan-related molecule, a TGF-beta superfamily member, a Wnt-related molecule, a receptor ligand, a T-cell target, a Dendritic cell target, an NK cell target, a monocyte/macrophage cell target and an angiogenesis target"; [0160] "peptide compositions advantageously arrange a second binding domain C-terminal to the effector domain"); and a domain comprising an Fc region (para [0054] "Placement of a constant sub-region (with a scorpion linker attached C-terminal to the constant region) in the interior of a polypeptide"; [0108] "linker 1 refers to any potential linker or hinge like peptide between the N-terminal proximal BD 1 and the "effector function domain", indicated as EFD. This subdomain is usually an engineered form of the Fc domain of human IgG1, but may include other subdomains with one or more effector functions"); wherein the recombinant bispecific antibody induces greater immune cell activation when the recombinant antibody construct is bound to the tumor associated antigen and/or to the antigen on the antigen presenting cell (para [0162] "The compositions described herein are capable of binding two targets simultaneously utilizing the pairs of binding domains at the N- and C-terminus of the molecule. In so doing, for cell-surface targets, the composition can `cross-link` or cause the physical co-approximation of the targets. It can be appreciated by those skilled in the art, that many receptor systems are activated upon such cross-linking and induced to signal, causing changes in cellular phenotype. The design of the compositions disclosed herein was intentionally chosen in part to maximize such signaling and control the resultant phenotype"), yet does not specifically teach an immune-stimulatory compound attached to the recombinant bispecific antibody by a linker.

Kischel teaches a multispecific recombinant antibody construct, comprising a target antigen binding domain, wherein the target antigen binding domain specifically binds to a tumor associated antigen (para [0020] "the ability of the first and/or second binding domains of the bispecific single chain antibody as defined herein to discriminate between the respective first and/or second molecule"; [0022] "The second binding domain of the bispecific single chain antibodies as defined herein binds to a cell surface antigen, preferably a tumor antigen"), attached to an immune-stimulatory compound (para [0123]-[0124] "use of a bispecific single chain antibody as defined hereinabove or as produced by the process as defined hereinabove...said CAIX constructs may be used for the treatment of renal or cervical carcinomas. In another preferred embodiment of the uses or methods of the invention, said pharmaceutical composition as defined hereinabove is suitable to be administered in combination with an additional drug, i.e. as part of a co-therapy. In said co-therapy, an active agent may be optionally included in the same pharmaceutical composition as the bispecific single chain antibody...In the case that the additional drug is a proteinaceous compound, it is advantageous that the proteinaceous compound be capable of providing an activation signal for immune effector cells"). Since the immune-stimulatory compound is added to the recombinant bispecific antibody of Kischel to enhance therapeutic efficacy (para [0124]), it would have been obvious to one of ordinary skill to have attached an immune-stimulatory compound to the recombinant bispecific antibodies taught by Emergent by a linker, in order to enhance therapeutic efficacy of the recombinant protein.

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I-II inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

NOTE, claims 6-59, 61-67, 75-99, 108-130 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).