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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2013 (21.11.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/173761 A3

(51) International Patent Classification:
C07K 16/28 (2006.01)

(21) International Application Number:
PCT/US2013/041656

(22) International Filing Date:
17 May 2013 (17.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/649,147 18 May 2012 (18.05.2012) US
61/792,619 15 March 2013 (15.03.2013) US

(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **SMITH, Dirk E.**; 11633 Meadowmeer Circle NE, Bainbridge Island, Washington 98110 (US). **FOLTZ, Ian**; 2108 Knightswood Place, Burnaby, BC V5A 4B9 (CA). **KING, Chadwick T.**; 1325 Moody Avenue, North Vancouver, BC V7L 3T5 (CA). **LIM, Ai Ching**; 7105 82nd Avenue SE, Mercer Island, Washington 98040 (US). **CLARK, Rutilio**; 5335 Old Mill Road NE, Bainbridge Island, Washington 98110 (US). **COMEAU, Michael R.**; 1044 High School Road NE, Bainbridge Island, Washington 98110 (US). **KETCHEM, Randal R.**; 6332 152nd Street SE, Snohomish, Washington 98296 (US). **SHI, Donghui**; 3198 Rickey Court, Thousand Oaks, California 91362 (US). **MIN, Xiaoshan**; 2108 Clarice Lane, Burlingame, California 94010 (US). **WANG, Zhulun**; 660 Glenbrook Drive, Palo Alto, California 94306 (US).

(74) Agent: **WRONA, Thomas J.**; Amgen Inc., 1201 Amgen Court W., Seattle, Washington 98119-3105 (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, 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, KM, 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,

[Continued on next page]

(54) Title: ST2 ANTIGEN BINDING PROTEINS

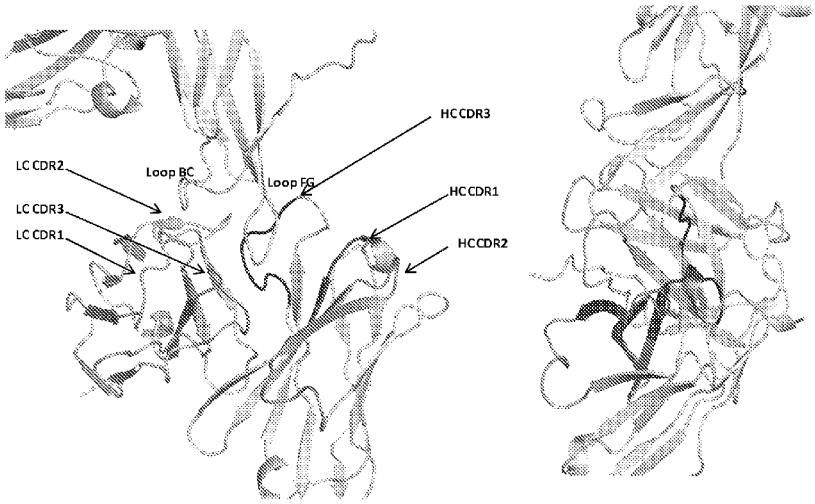

FIG. 8

(57) Abstract: Described herein are compositions and methods related to antigen binding proteins that bind to human ST2, including antibodies. In particular embodiments, the disclosure provides fully human anti-ST2 antibodies and derivatives and variants thereof. Further provided are nucleic acids encoding such antibodies and antibody fragments, variants, and derivatives. Also, provided are methods of making and using such antibodies including methods of treating and preventing autoimmune and inflammatory disorders.

WO 2013/173761 A3

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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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:
20 February 2014

International application No.
PCT/US2013/041656

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/28 (2013.01)
USPC - 424/143.1
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)
IPC(8) - A61K 39/395; C07K 16/18, 16/28; C12N 1/21, 5/10, 5/16, 15/00, 15/11; C12P 21/08 (2013.01)
USPC - 424/141.1, 142.1, 143.1; 435/252.3, 320.1, 331, 332, 334; 530/387.1, 387.3, 387.9, 388.15, 388.22; 536/23.53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 38/00, 2039/505; C07K 2317/21; C12N 15/86 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0221257 A1 (CAMPBELL et al) 02 September 2010 (02.09.2010) entire document	113
A	US 2010/0247545 A1 (BEDIAN et al) 30 September 2010 (30.09.2010) entire document)	1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141
A	US 2010/0247442 A1 (COTTY et al) 30 September 2010 (30.09.2010) entire document	1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141
A	US 2009/0214559 A1 (VARNUM et al) 27 August 2009 (27.08.2009) entire document	1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141
A	US 2011/0256635 A1 (SNIDER) 20 October 2011 (20.10.2011) entire document	1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141
A	US 2005/0058639 A1 (GUDAS et al) 17 March 2005 (17.03.2005) entire document	1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141

☐ 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
02 December 2013	20 DEC 2013
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: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041656

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:

Specifically, SEQ ID NOs 7, 8, 29, 30, 40, 41, 51, 52, 62, 63, 73, 74, 95, 96, 106, 107, 117, 118, 128, and 129 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/041656

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, 8, 38-58, 75-112, 114, 115, 122, 125, 142-154
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:

See Extra Sheets

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.:

1-6, 9-13, 59-74, 113, 116-121, 123, 124, 126-141, limited to SEQ ID NOs: 7; 8, 29, 30, 40, 41, 51, 52, 62, 63, 73, 74, 95, 96, 106, 107, 117, 118, 128, and 129

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.:

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

International application No.
PCT/US2013/041656

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 need to be paid.

Group I+: claims 1-6, 9-37, 59-74, and 135-141 are drawn to an isolated ST2 antigen binding protein comprising: a) a light chain variable domain having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:163, SEQ ID NO:164, or SEQ ID NO:165; b) a heavy chain variable domain having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:145, SEQ ID NO:146, or SEQ ID NO:147; or c) a light chain variable domain of a) and a heavy chain variable domain of b).

Group II: claims 113, 116-121, 123, 124, and 126-134 are drawn to an isolated ST2 antigen binding protein, wherein the ST2 antigen binding protein crosscompetes with: an antibody comprising a light chain comprising the amino acid sequence set forth in SEQ ID:85 and a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 19; or an antibody comprising a light chain comprising the amino acid sequence set forth in SEQ ID NO:93 and a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:27 an isolated ST2 antigen binding protein that binds a polypeptide comprising human ST2 domain 1 and domain 2, wherein binding is significantly inhibited when a single mutation is introduced into human ST2 domain 1 or domain 2 of the polypeptide, wherein the single mutation is L14R, 115R, S33R, E43R, V47R, A62R, G65R, T79R, D92R, D97R, V104R, G138R, N152R, or V176R; an isolated ST2 antigen binding protein, wherein said ST2 antigen binding protein binds within amino acids 33-44 or 88-94 of SEQ ID NO: 1 as determined by hydrogen/deuterium exchange analysis; an isolated ST2 antigen binding protein which binds to ST2 creating an interface, wherein the interface created by said binding comprises ST2 residue K1, F2, P19, R20, Q21, G22, K23, Y26, 170, V71, R72, S73, P74, T75, F76, N77, R78, T79, or Y81.

The first invention of Group I+ is restricted to an isolated ST2 antigen binding protein comprising a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:95, encoded by SEQ ID NO:73, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:106, CDR2 is selected to be SEQ ID NO:117, and CDR3 is selected to be SEQ ID NO:128; and a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:29, encoded by SEQ ID NO:7, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:40, CDR2 is selected to be SEQ ID NO:51, and CDR3 is selected to be SEQ ID NO:62 (antibody "Ab1"). It is believed that claims 1-6, 9-11, and 59-74 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 7, 29, 40, 51, 62, 73, 95, 106, 117, and 128.

Applicant is invited to elect additional isolated ST2 antigen binding proteins with specified SEQ ID NOs for each heavy and light chain CDR1, 2, and 3 to be searched in a specific combination by paying additional fees for each set of election. An exemplary election would be an isolated ST2 antigen binding protein comprising a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:97, encoded by SEQ ID NO:75, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:108, CDR2 is selected to be SEQ ID NO:119, and CDR3 is selected to be SEQ ID NO:130; and a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:31, encoded by SEQ ID NO:9, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3, where CDR1 is selected to be SEQ ID NO:42, CDR2 is selected to be SEQ ID NO:53, and CDR3 is selected to be SEQ ID NO:64 (antibody "Ab3"). Additional isolated ST2 antigen binding proteins will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further 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.

The inventions listed in Groups I+ and II 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+, an isolated ST2 antigen binding protein comprising a light chain variable domain of SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:163, SEQ ID NO:164, or SEQ ID NO:165 and a heavy chain variable domain of SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:145, SEQ ID NO:146, or SEQ ID NO:147, are not found in Group II; the special technical features of Group II, an isolated ST2 antigen binding protein that binds a polypeptide comprising human ST2 domain 1 and domain 2, wherein binding is significantly inhibited when a single mutation is introduced into the polypeptide, are not found in Groups I+.

The Groups I+ and II share the technical features of an isolated ST2 antigen binding protein that binds a polypeptide comprising human ST2. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2011/0256635 A1 to Snider discloses an isolated ST2 antigen binding protein that binds a polypeptide comprising human ST2 (described herein are antibodies and antigen-binding fragments of antibodies that bind to human soluble Growth Stimulation-Expressed Gene 2 (ST2) protein, Para. [0002]; provided herein are isolated antibodies and antigen-binding fragments thereof, Para. [0005]).

The Groups I+ antibodies do not share a significant structural element responsible for binding a ST2 antigen, requiring the selection of alternatives for the light and heavy chain variable regions of the antibody, where "a light chain variable domain having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:163, SEQ ID NO:164, or SEQ ID NO:165" and "a heavy chain variable domain having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:145, SEQ ID NO:146, or SEQ ID NO:147."

The Groups I+ share the technical features of an isolated ST2 antigen binding protein comprising a light chain variable region, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3; and a heavy chain variable region, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3; further comprising a nucleotide sequence encoding the light chain variable region and a nucleotide sequence encoding the heavy chain variable region. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2011/0256635 A1 to Snider discloses an isolated ST2 antigen binding protein (described herein are antibodies and antigen-binding fragments of antibodies that bind to human soluble Growth Stimulation-Expressed Gene 2 (ST2) protein, Para. [0002]; provided herein are isolated antibodies and antigen-binding fragments thereof, Para. [0005]) comprising a light chain variable region, the light chain further comprising light chain complementary determining regions CDR1, CDR2, and CDR3; and a heavy chain variable region, the heavy chain further comprising heavy chain complementary determining regions CDR1, CDR2, and CDR3 (an antibody or fragment described herein comprises the heavy and/or light chain variable region, Para. [0069]; there are three CDRs termed CDR1, CDR2, and CDR3 within each VL and each VH, Para. [0033]; an antibody or fragment described herein contains one or more, e.g., one, two, three, four, five, or six, CDRs of the light and/or heavy chain, Para. [0070]); further comprising a nucleotide sequence encoding the light chain variable region and a nucleotide sequence encoding the heavy chain variable region (a nucleic acid molecule encoding a polypeptide comprising the heavy and/or light chain of the antibody ...or a nucleic acid encoding one or more, e.g., one, two, or three, of the CDR regions of the heavy or light chain, Para. [0078]).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.