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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
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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,
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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:**
7 January 2016

(54) **Title:** IMMUNOTHERAPY WITH BINDING AGENTS

(57) **Abstract:** Binding agents that modulate the immune response are disclosed. The binding agents may include antibodies, soluble receptors, and/or polypeptides. Also disclosed are methods of using the binding agents for the treatment of diseases such as cancer.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/30472

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395, C07K 16/00, C12N 5/07 (2015.01)

CPC - A61K 38/00, A61K 2039/505

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 16/00, C12N 5/07 (2015.01)

CPC: A61K 38/00, A61K 2039/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/130.1, 435/330, 530/387.7Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms: V-set and transmembrane domain containing protein 4, VSTM4, C10orf72, Ig domain, IG-like, Ig V-type domain, signal sequence, mouse, human, membrane protein, extracellular domain, antibody, monoclonal, polyclonal, single chain, B7-H4/VSTM4 pathway, soluble receptor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0067882 A1 (ALSOBROOK et al.) 08 April 2004 (08.04.2004) para [0032], [0164], [0165], Tables 19C, 19E, SEQ ID NO: 76	1-7

☐ 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

29 September 2015 (29.09.2015)

Date of mailing of the international search report

28 OCT 2015

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/30472

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.: 8, 16-34, 41-61, 64-68, 74-79
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 Supplemental Sheet to continue *****

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.:
1-7

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/US 15/30472

Continuation of 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.

Group I: Claims 1-7, drawn to antibody that specifically binds the extracellular domain of V-set and transmembrane domain containing protein 4 (VSTM4).

Group II: Claims 9-15, drawn to a soluble receptor comprising the extracellular domain or VSTM4 fragments thereof.

Group III: Claims 35-40, 62-63, 69-73, drawn to agents which disrupt signaling from a B7-H4/VSTM4 pathway by binding to VSTM4 or B7-H4, thereby disrupting B7-H4 activation of VSTM4 signaling.

The inventions listed as Groups I through III 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

Groups II and III do not require an antibody that specifically binds the extracellular domain of VSTM4, as required by group I.

Groups I and III do not require a soluble receptor comprising the extracellular domain of VSTM4, as required by group II.

Group I and II do not require an agent that disrupts signaling from a B7-H4/VSTM4 pathway, as required by group III.

Common technical features

Groups I, II and III include the common technical feature of polypeptides comprising the extracellular domain of VSTM4 and sub-domains comprising portions of said extracellular domain.

Groups I and III share the common technical feature of an agent that specifically bind to the extracellular domain of VSTM4.

However, these shared technical features do not represent a contribution over prior art, because the shared technical features are anticipated by US 2004/0067882 A1 to Alsobrook, II. et al. (hereinafter Alsobrook).

Alsobrook discloses VSTM4 polypeptides, fragments of said polypeptides, and antibodies [agents] that bind specifically to said peptides (abstract "Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies that immunospecifically bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the novel polypeptide, polynucleotide, or antibody specific to the polypeptide."), Alsobrook further discloses SEQ ID NO:76, a polypeptide comprising 100% identity to the claimed SEQ ID NO: 3, cited by the applicant as Human VSTM4 extracellular domain (AA24-AA180). Alsobrook further discloses therapeutic antibodies (para [0009] "nucleic acids and polypeptides ... and fragments thereof, will hereinafter be collectively designated as "NOVX" nucleic acid or polypeptide sequences.", para [0032] "The invention further provides an antibody that binds immunospecifically to a NOVX polypeptide. The NOVX antibody may be monoclonal, humanized, or a fully human antibody. ... More preferably, the NOVX antibody neutralizes the activity of the NOVX polypeptide.", para [0033] "the invention provides for the use of a therapeutic in the manufacture of a medicament for treating a syndrome associated with a human disease, associated with a NOVX polypeptide. Preferably the therapeutic is a NOVX antibody.").

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

Groups I through III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.