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(71) **Applicant** *(for all designated States except US)*: **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; 3160 Chestnut Street, Suite 200, Philadelphia, Pennsylvania 19104-6283 (US).

(71) **Applicant** *(for all designated States except US)*: **INOVIO PHARMACEUTICALS, INC.** [US/US]; 1787 Sentry Parkway West, Building 18, Suite 400, Blue Bell, Pennsylvania 19422 (US).

(72) **Inventors; and**
(71) **Applicants** *(for US only)*: **WEINER, David B** [US/US]; 717 Beacom Lane, Merion, Pennsylvania 19066 (US). **MUTHUMANI, Karupiah** [US/US]; 52 Ivy Lane, Cherry Hill, New Jersey 08002 (US). **SARDESAI, Niranjan** [US/US]; 480 Mallard Circle, Blue Bell, Pennsylvania 19422 (US). **FLINGAI, Seleeke** [US/US]; 1623 Penn North Avenue, Minneapolis, Minnesota 55411 (US).

(74) **Agent**: **KIM, Thomas**; c/o Inovio Pharmaceuticals, Inc., 1787 Sentry Parkway West, Building 18, Suite 400, Blue Bell, Pennsylvania 19422 (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, IR, IS, JP, KE, KG, 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, 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.

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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**:
31 July 2014

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(54) **Title**: DNA ANTIBODY CONSTRUCTS AND METHOD OF USING SAME

(57) **Abstract**: Disclosed is a composition including a recombinant nucleic acid sequence that encodes an antibody. Also disclosed is a method of generating a synthetic antibody in a subject by administering the composition to the subject. The disclosure also provides a method of preventing and/or treating disease in a subject using said composition and method of generation.

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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 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:

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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.: 48-50
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.

Groups I+, claims 1-47, 51-52, drawn to a method of generating a synthetic antibody in a subject, the method comprising administering to the subject a composition comprising a recombinant nucleic acid sequence encoding an antibody or fragment thereof; or a composition comprising a first recombinant nucleic acid sequence encoding a heavy chain polypeptide, or fragment thereof, and a second recombinant nucleic acid sequence encoding a light chain polypeptide, or fragment thereof; or using the method for preventing or treating a disease in a subject; as well as the product produced by the method. The first invention is restricted to the recombinant nucleic acid further comprises a promoter that is CMV, and the method is directed to treating HIV and SEQ ID NOs: 1 and 3-4 (Specification: para [00292] - SEQ ID NO: 3, VH-CH1; and SEQ ID NO: 4, VL-CL). Group I+ will be searched to the extent that it reads on the recombinant nucleic acid further comprises a promoter that is CMV and SEQ ID NOs: 1 and 3-4, without fee. It is believed that claims 1-6, 10-15, 19-27, 31-37, 51 read on this first named invention. **********Continued in the 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.:
1-6, 10-15, 19-27, 31-37, and 51, limited to SEQ ID NOs: 1 and 3-4.

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.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 48/00; A61K 39/395; A61K 39/00; C07H 21/04 (2014.01)
USPC - 514/44R; 424/130.1; 424/133.1; 536/23.53
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 48/00; A61K 39/395; A61K 39/00; C07H 21/04; A61K 39/42 (2014.01)
USPC - 514/44R; 424/130.1; 424/133.1; 536/23.53; 424/159.1, 424/160.1; 424/174.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 48/00; A61K 39/395; A61K 39/00; C07H 21/04; A61K 39/42 (2014.01) - see keyword below
USPC - 514/44R; 424/130.1; 424/133.1; 536/23.53; 424/159.1, 424/160.1; 424/174.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: vector, cassette, construct, expressing, encoding, antibody, HIV, synthesize, heavy chain, light chain, promoter, CMV, antigen, cytomegalovirus, constant, CH1, CH2, CH3, CL, VRC02, VRC01, VRC03, scFV, C.gamma.1, polynucleotide, nucleic acid, pharmaceutical, composition, pathogen, treating,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- A	US 2012/0282264 A1 (MASCOLA et al.) 08 November 2012 (08.11.2012), para [0003], [0041-[0043], [0101], [0102], [0127]-[0130], [0133], [0134], [0162], [0164], [0166], [0170], [0188], [0191], [0221], [0238], [0249], [0253], [0271], [0274]-[0276], [0300], [0305], [0312], [0350], [0366], [0371], [0434], and [0484]	1-6, 10-15, 21-27, 31-35, and 51 ---------- 19-20, 36-37
A	US 2012/0269723 A1 (BRINKMANN et al.) 25 October 2012 (25.10.2012), Abstract, para [0288], and SEQ ID NO: 44 (943 a.a.), amino acid residues betweeen 1-678	19, 36
A	US 2012/0232133 A1 (BALAZS et al.) 13 September 2012 (13.09.2012), para [0135], and SEQ ID NO: 24 (6418 nt), nucleotides between 1237-1969 and 2805-3450	20, 37
A	KIM et al. Two-promoter vector is highly efficient for overproduction of protein complexes. Protein Sci. 2004, Vol. 13(6), p..1698-1703. Abstract; pg 1700, Fig 1; and pg 1701, Fig 3	10-12, 23-24,
A	ELLISON et al.. The nucleotide sequence of a human immunoglobulin C.gamma.1 gene. Nucleic Acids Res. 1982, Vol. 10(13), p. 4071-4079. Abstract	13-14, 25-26
A	NCHU_Administrator, Microsoft PowerPoint - week 3 Antibody structure Ag-Ab interactions, NCHU, Power Point, 2007 [online]. [Retrieved on 2014.02.12]. Retrieved from the Internet: <URL: http://www.as.nchu.edu.tw/lab/5c/course/antibody/week%203%20Antibody%20structure%20Ag-Ab%20interactions.pdf> pg 1-44, pg 6, Antibody structure by modern techniques	13-14, 25-26

☒ 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
14 February 2014 (14.02.2014)	20 MAY 2014
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FANG et al. An antibody delivery system for regulated expression of therapeutic levels of monoclonal antibodies in vivo. Mol Ther. 2007, Vol. 15(6), p. 1153-9. Entire documentation, especially Abstract.	1-6, 10-15, 19-27, 31-37, 51

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Continuation of:
Box No III (unity of invention is lacking)

Applicants must 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. An exemplary election would be: 1) wherein the recombinant nucleic acid sequence further comprises a third nucleic acid sequence encoding a protease cleavage sites (1-15, 91-27, 31-37, 51); or 2) treating CHIKV, directed to SEQ ID NOs: 58-61 (claims 1-6, 10-15, 21-27, 31-34, 38-40, 51).

The inventions listed as Groups I+ 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 Feature
Among Groups I+, each additional nucleic acid encoding a third element is structurally and functionally different from all other nucleic acids encoding a third element; and the method for treating each disorder requires a functionally different antibody, and each SEQ ID NO represents a structurally different nucleotide or protein sequence; and each antibody is structurally different from all others.

Common Technical Features
The inventions of Groups I+ share the technical feature of generating a synthetic antibody in a subject, comprising administering to the subject a composition comprising a recombinant nucleic acid sequence encoding an antibody or fragment thereof, wherein the recombinant nucleic acid sequence is expressed in the subject to generate the synthetic antibody; or
comprising administering to the subject a composition comprising a first recombinant nucleic acid sequence encoding a heavy chain polypeptide, or fragment thereof, and a second recombinant nucleic acid sequence encoding a light chain polypeptide, or fragment thereof, wherein the first recombinant nucleic acid sequence is expressed in the subject to generate a first polypeptide and the second recombinant nucleic acid is expressed in the subject to generate a second polypeptide, wherein the synthetic antibody is generated by the first and second polypeptides; and
a method of preventing or treating a disease in a subject, comprising generating a synthetic antibody in a subject.

The inventions of claims 31-47 of Groups I+ further share the technical feature of preventing or treating a disease in a subject, comprising generating a synthetic antibody in a subject.

The inventions of Claims 19-20 and 36-37 of Groups I+ further share the technical feature of a nucleic acid encoding an antibody for treating or preventing HIV.

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2012/0282264 A1 to MASCOLA et al. (hereinafter 'Mascola') as follows:

Mascola discloses a method of generating a synthetic antibody in a subject (para [0350] - 'administration of the antibody results in a reduction in the establishment of HIV infection and/or reducing subsequent HIV disease progression in a subject...administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody', wherein 'administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody' is for 'generating a synthetic antibody in a subject')
---- the method comprising administering to the subject a composition comprising a recombinant nucleic acid sequence encoding an antibody or fragment thereof, wherein the recombinant nucleic acid sequence is expressed in the subject to generate the synthetic antibody (para [0350] - 'administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody, thereby preventing or treating the HIV-1 infection'; para [0305] - 'Any of the nucleic acids encoding any of the antibodies, V.sub.H and/or V.sub.L, ...or fragment... can be expressed'; para [0166]; para [0366] - 'Plasmids including nucleic acid sequences encoding the VRC03 heavy chain and VRC03 light chain'; para [0345] - 'Compositions ... antibodies that specifically bind gp120 ... functional fragments'; para [0484] - 'treat HIV in a human subject by administration ...gp120...human neutralizing mAbs' para [0253] - 'a novel class of gp120 antibodies, ... VRC03').
Mascola further discloses using a cytomegalovirus (CMV) promoter for antibody expression (para [0312] - 'The expression of nucleic acids encoding the isolated proteins...The promoter can be any promoter of interest, including a cytomegalovirus promoter').

Mascola discloses a method of generating a synthetic antibody in a subject (para [0350] - 'administration of the antibody results in a reduction in the establishment of HIV infection and/or reducing subsequent HIV disease progression in a subject...administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody', wherein 'administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody' is for 'generating a synthetic antibody in a subject'), the method comprising
---administering to the subject a composition comprising a first recombinant nucleic acid sequence encoding a heavy chain polypeptide, or fragment thereof, and a second recombinant nucleic acid sequence encoding a light chain polypeptide, or fragment thereof (para [0350] - 'administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody, thereby preventing or treating the HIV-1 infection'; para [0305] - 'Any of the nucleic acids encoding any of the antibodies, V.sub.H and/or V.sub.L, ...or fragment... can be expressed'; para [0166]; para [0042] - 'VRC01 precisely targets the CD4-defined site of vulnerability on HIV-1 gp120'),
---wherein the first recombinant nucleic acid sequence is expressed in the subject to generate a first polypeptide and the second recombinant nucleic acid is expressed in the subject to generate a second polypeptide, wherein the synthetic antibody is generated by the first and second polypeptides (para [0305] - 'Any of the nucleic acids encoding any of the antibodies, V.sub.H and/or V.sub.L, ...or fragment... can be expressed'; para [0366] - 'Plasmids including the nucleic acids encoding VRC01 heavy chain, VRC01 light chain, ...were deposited ...VRC01 heavy chain... PTA-10412, VRC01 light chain ...PTA-10411'; para [0042] - 'VRC01 precisely targets the CD4 -defined site of vulnerability on HIV-1 gp120', wherein ' VRC01' indicating 'wherein the synthetic antibody is generated by the first and second polypeptides').

**********Continued in the next extra sheet**********

Continuation of:
The previous extra sheet - Box No III (unity of invention is lacking)

Mascola further discloses a method of preventing or treating a disease in a subject, the method comprising generating a synthetic antibody in a subject (para [0350] - 'administering to the subject a therapeutically effective amount of ... a nucleic acid encoding the antibody, thereby preventing or treating the HIV-1 infection'; para [0305] - 'Any of the nucleic acids encoding any of the antibodies, V.sub.H and/or V.sub.L, ...or fragment... can be expressed'; para [0166]; para [0366] - "Plasmids including the nucleic acids encoding VRC01 heavy chain, VRC01 light chain...Plasmids including nucleic acid sequences encoding the VRC03 heavy chain and VRC03 light chain'; para [0253] - 'a novel class of gp120 antibodies, as exemplified by VRC01, ...VRC03'; para [0170] - 'an antigen is derived from HIV, such as a gp120 polypeptide').

Furthermore, Mascola further discloses a nucleic acid encoding an antibody for treating or preventing HIV (para [0253] - 'a novel class of gp120 antibodies, as exemplified by VRC01, ...VRC03'; para [0170] - 'an antigen is derived from HIV, such as a gp120 polypeptide'; Para [0129]-[0130] - ' the nucleic acid sequence of the heavy chain of gp120-specific antibody VRC01... the nucleic acid sequence of the light chain of gp120-specific antibody VRC01'; para [0101] -[0102] - 'heavy chain of gp120-specific antibody VRC01... the light chain of gp120-specific antibody VRC01'; para [0133]-[0134] - the nucleic acid sequence of the heavy chain of gp120-specific antibody VRC03....the nucleic acid sequence of the light chain of gp120-specific antibody VRC03'; para [0127]-[0128] - 'the amino acid sequence of the heavy chain of gp120-specific antibody VRC03....the amino acid sequence of the light chain of gp120-specific antibody VRC03'; para [0336])

Without a shared special technical feature, the inventions lack unity with one another.

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

Note re item 4: Claims 48-50 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.