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KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
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- (88) **Date of publication of the international search report:**
22 January 2015

(54) **Title:** IMMUNOGENIC WT-1 PEPTIDES AND METHODS OF USE THEREOF

(57) **Abstract:** This invention provides peptides, immunogenic compositions and vaccines, and methods of treating, reducing the in-
cidence of, and inducing immune responses to a WT-1 -expressing cancer, comprising peptides derived from the WT-1 protein.



WO 2013/106834 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/21448

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00, A61K 38/08 (2013.01)

USPC - 424/185.1, 514/21.6

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)

USPC- 424/185.1, 514/21.6

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

USPC- 424/184.1, 530/328

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google, Google Scholar, PubMed: WT1 protein, Wilms tumour, peptide, fragment, epitope, immunodominant, Rankpep, Immune Epitope Database, immunogenic, T-cell response
 GenCore 6.4.1: SEQ ID NO: 147

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0034842 A1 (Graddis, et al.) 11 February 2010 (11.02.2010) para [0016], [0021], [0034], [0043]-[0046], [0234]-[0242], [0400]-[0407], [0411], [0421], [0449], [0450], [0567], [0495], [0502], [0529], [0559], [0563]-[0564], Table 29, SEQ ID NO: 724	1, 5, 7, 8, and 15
A	THE MGC PROJECT TEAM; UniProt Accession Q6PI38; 14 December 2011; [online]; available on the internet: <http://www.uniprot.org/uniprot/Q6PI38.txt?version=42>; downloaded on 7 May 2013.	1, 5, 7, 8, and 15
A	US 7,597,894 B2 (Graddis, et al.) 06 October 2009 (06.10.2009) Example 32, Fig 8, SEQ ID NO: 724	1, 5, 7, 8, and 15
A	Bellantuono, et al. Two distinct HLA-A0201-presented epitopes of the Wilms tumor antigen 1 can function as targets for leukemia-reactive CTL. Blood 2002, 100(10):3835-3837; Abstract, pg 3835, col 2	1, 5, 7, 8, and 15
A	Ochsenreither, et al. Wilms' tumor protein 1 (WT1) peptide vaccination in AML patients: predominant TCR CDR3- sequence associated with remission in one patient is detectable in other vaccinated patients. Cancer Immunol Immunother. Epub 2011 Sep 7, 61(3):313-322	1, 5, 7, 8, and 15
A	Sloand, et al. T-cell immune responses to Wilms tumor 1 protein in myelodysplasia responsive to immunosuppressive therapy. Blood Epub 19 November 2010, 117(9):2691-2699; Abstract, pg 2692, col 1	1, 5, 7, 8, and 15

☒ 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

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22 MAY 2013

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INTERNATIONAL SEARCH REPORT

International application No.

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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	Rezvani, et al. T-cell responses directed against multiple HLA-A*0201-restricted epitopes derived from Wilms' tumor 1 protein in patients with leukemia and healthy donors: identification, quantification, and characterization. Clin Cancer Res. 2005, 11(24 Pt 1):8799-807; Abstract, pg 8799, col 1; pg 8800, col 1	1, 5, 7, 8, and 15
A	May, et al. Peptide epitopes from the Wilms' tumor 1 oncoprotein stimulate CD4+ and CD8+ T cells that recognize and kill human malignant mesothelioma tumor cells. Clin Cancer Res. 2007, 13(15 Pt 1):4547-55; Abstract, pg 4547, Table 1	1, 5, 7, 8, and 15
A	Borbulevych, et al. Structures of native and affinity-enhanced WT1 epitopes bound to HLA-A*0201: implications for WT1-based cancer therapeutics. Mol Immunol. 2010, 47(15):2519-24; Abstract	1, 5, 7, 8, and 15
A	Lehe, et al. The Wilms' tumor antigen is a novel target for human CD4+ regulatory T cells: implications for immunotherapy. Cancer Res. 2008, 68(15):6350-6459; Abstract, Supplemental Table 2	1, 5, 7, 8, and 15
A	Pinilla-Ibarz, et al. Improved human T-cell responses against synthetic HLA-0201 analog peptides derived from the WT1 oncoprotein. Leukemia. 2006, 20(11):2025-33; Abstract, pg 2026, Table 1	1, 5, 7, 8, and 15
A	Fujiki, et al. A WT1 protein-derived, naturally processed 16-mer peptide, WT1(332), is a promiscuous helper peptide for induction of WT1-specific Th1-type CD4(+) T cells. Microbiol Immunol. 2008, 52(12):591-600; Abstract, pg 592, 1st col	1, 5, 7, 8, and 15
A	Sugiyama. WT1 (Wilms' tumor gene 1): biology and cancer immunotherapy. Jpn J Clin Oncol. 2010, 40(5):377-87	1, 5, 7, 8, and 15
X,P	Dobrovina, et al. Mapping of novel peptides of WT-1 and presenting HLA alleles that induce epitope-specific HLA-restricted T cells with cytotoxic activity against WT-1(+) leukemias. Blood Epub 23 May 2012, 120(8):1633-46; Abstract, pg 1637, Table 1, entry 13	1, 5, 7, 8, and 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 13/21448

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.: 9-14 and 16
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.

Group I+: claims 1-8 and 15, drawn to an isolated WT-1 peptide consisting of a specific amino acid sequence, and a method of using said peptide. The first invention (claims 1, 5, 7, 8, and 15) is restricted to SEQ ID NO:147. Should an additional fee(s) be paid, Applicant is invited to elect an additional SEQ ID NO(s) to be searched.

The inventions listed as Group 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:

***** 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, 5, 7, 8, and 15, restricted to SEQ ID NO:147

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 13/21448

***** Supplemental Sheet *****

In Continuation of Box III. Observations where unity of invention is lacking:

The inventions of Group I+ share the technical feature of an isolated WT-1 peptide. However, this shared technical feature does not represent a contribution over prior art as being anticipated by an article titled "A WT1 protein-derived, naturally processed 16-mer peptide, WT1(332), is a promiscuous helper peptide for induction of WT1-specific Th1-type CD4(+) T cells" by Fujiki, et al. (Microbiol Immunol. 2008, 52(12):591-600) (hereinafter "Fujiki") that discloses an isolated WT-1 peptide (pg 592, 1st col, last para, "WT1(332) peptide (KRYFKLSHLQMHSRKH)... was synthesized"; Abstract, "A WT1 protein-derived 16-mer peptide, WT1(332) ... can induce WT1(332)-specific CD4(+) T cell responses with the restriction of not only HLA-DRB1*0405 but also HLA-DRB1*1501, -DRB1*1502, or -DPB1*0901... These results indicate that the natural peptide, WT1(332), is a promiscuous WT1-specific helper epitope. WT1(332) is expected to apply to cancer patients with various types of HLA class II as a WT1-specific helper peptide in combination with HLA class I-restricted WT1 peptides"). As said peptide was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is the specific amino acid sequence recited therein. The inventions do not share a special technical feature, because the claimed amino acid sequence SEQ ID NO: 147 was known in the art at the time of the invention, as evidenced by US 2005/0112134 A1 to Graddis, et al. (SEQ ID NO 724, amino acids 56-64, 100% identity). Thus, no significant structural similarities can readily be ascertained among the amino acid sequences. 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.