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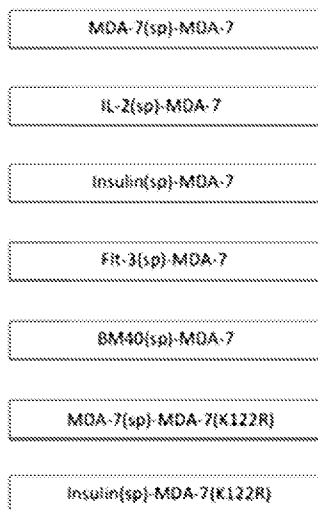
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(54) Title: MDA-7/IL SECRETORY VARIANTS AND METHODS OF USE

FIG. 1



(57) Abstract: In various aspects, the present disclosure provides polynucleotides encoding a fusion protein, as well as vectors, cells, and compositions comprising the same. In embodiments, the fusion protein includes an insulin signal peptide and an MDA-7/IL-24 protein. Methods of using the polynucleotides, vectors, cells, and compositions, such as in the treatment or prevention of cancer, are also provided.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/14686

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - A61K 38/17, 39/395, 48/00; C07H 21/04; C07K 14/82, 16/30 (2019.01)
 CPC - A61K 38/00, 38/17, 45/06, 48/005; C07K 14/47, 14/52, 14/54, 16/244; C12N 15/86; G01N 33/5011

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.
Y	US 2006/0292157 A1 (FISHER et al.) 28 December 2006; paragraphs [0015], [0026], [0035], [0043], [0101], [0103], [0130], [0132], [0147], [0148]; claims 35, 49, 63 US 2006/0062772 A1 (KEEGAN et al.) 23 March 2006; paragraph [0060]; Table 1; claim 1	1-2, 5-6, 8, 12/1-2, 12/5-6, and 12/8, 13/12/1-2, 13/12/5-6, 13/12/8, 14/12/1-2, 14/12/5-6, 14/12/8, 15/14/12/1-2, 15/14/12/5-6, 15/14/12/8, 16/15/14/12/1-2, 16/15/14/12/5-6, 16/15/14/12/8, 17/15/14/12/1-2, 17/15/14/12/5-6, 17/15/14/12/8, 18/17/15/14/12/1-2, 18/17/15/14/12/5-6, 18/17/15/14/12/8, 27/1-2, 27/5-6, 27/8, 30/27/1-2, 28/27/1-2, 28/27/5-6, 28/27/8, 30/27/5-6, 30/27/8, 31/30/27/1-2, 31/30/27/5-6, 31/30/27/8, 32/27/1-2, 32/27/5-6, 32/27/8, 33/27/1-2, 33/27/5-6, 33/27/8, 35-36, 39-40, 42

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

"D" document cited by the applicant in the international application

"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 15 August 2019 (15.08.2019)	Date of mailing of the international search report 03 SEP 2019
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 Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/14686

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0062772 A1 (KEEGAN et al.) 23 March 2006; paragraph [0060]; Table 1; claim 1	1-2, 5-6, 8, 12/1-2, 12/5-6, and 12/8, 13/12/1-2, 13/12/5-6, 13/12/8, 14/12/1-2, 14/12/5-6, 14/12/8, 15/14/12/1-2, 15/14/12/5-6, 15/14/12/8, 16/15/14/12/1-2, 16/15/14/12/5-6, 16/15/14/12/8, 17/15/14/12/1-2, 17/15/14/12/5-6, 17/15/14/12/8, 18/17/15/14/12/1-2, 18/17/15/14/12/5-6, 18/17/15/14/12/8, 27/1-2, 27/5-6, 27/8, 30/27/1-2, 28/27/1-2, 28/27/5-6, 28/27/8, 30/27/5-6, 30/27/8, 31/30/27/1-2, 31/30/27/5-6, 31/30/27/8, 32/27/1-2, 32/27/5-6, 32/27/8, 33/27/1-2, 33/27/5-6, 33/27/8, 35-36, 39-40, 42
Y	US 2014/0235702 A1 (WAYNE STATE UNIVERSITY et al.) 21 August 2014; paragraph [0040]	28/27/1-2, 28/27/5-6, 28/27/8, 29/28/27/1-2, 29/28/27/5-6, 29/28/27/8
Y	US 2012/0237533 A1 (KULIK et al.) 20 September 2012; paragraphs [0012], [0030]	30/27/1-2, 30/27/5-6, 30/27/8, 31/30/27/1-2, 31/30/27/5-6, 31/30/27/8
Y	US 2007/0009484 A1 (HUNT et al.) 11 January 2007; paragraphs [0039] [0472]	33/27/1-2, 33/27/5-6, 33/27/8
A	US 2009/0053244 A1 (CHEN et al.) 26 February 2009; paragraph [0575]	7, 12/7, 13/12/7, 14/12/7, 15/14/12/7, 16/15/14/12/7, 17/15/14/12/7, 18/17/15/14/12/7, 27/7, 28/27/7, 30/27/7, 31/30/27/7, 32/27/7, 33/27/7, 41

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/14686

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.: 19-26, 34
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:

-Please See Supplemental Page-

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.:

-Please See Supplemental Page-

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
Information on patent family members

International application No.

PCT/US19/14686

-***-Continued from Box No. III Observations where unity of invention is lacking: -***-

The polynucleotide, protein, vector, and method will be searched to the extent they encompass an MDA-7/IL-24 protein encompassing SEQ ID NO: 4 (first exemplary MDA-7/IL-24 amino acid sequence); a signal sequence encompassing SEQ ID NO: 5 (first exemplary signal sequence), and an encoding polynucleotide encompassing SEQ ID NO: 6 (first exemplary polynucleotide sequence). Applicant is invited to elect additional protein and/or signal peptide and/or associated polynucleotide sequence(s), with specified SEQ ID NO: for each, with specified substitution(s) or deletion(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable bases, residues or substituents), and available as an option within at least one searchable claim, to be searched. Additional protein, signal sequence, and/or associated encoding polynucleotide sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1, 2, 5, 6, 7 (in-part), 8, 12-18, 27-33, 35, 36, 39, 40, 41 (in-part), and 42 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 4 (MDA-7/IL-24), SEQ ID NO: 5 (signal peptide); and SEQ ID NO: 6 (polynucleotide). Applicants must specify the claims that encompass any additionally elected sequence(s). Applicants must further indicate, if applicable, the claims which encompass 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 an MDA-7/IL-24 protein encompassing SEQ ID NO: 3 (MDA-7/IL-24).

Groups I+ share the technical features including: a polynucleotide encoding a fusion protein, wherein the fusion protein comprises an insulin signal peptide and an MDA-7/IL-24 protein; a fusion protein encoded by the polynucleotide; a vector comprising the polynucleotide; a method of treating cancer, the method comprising administering to a subject in need thereof the polynucleotide.

However, these shared technical features are previously disclosed by US 2007/0009484 A1 to Hunt et al. (hereinafter 'Hunt') in view of US 2006/0062772 A1 to Keegan et al. (hereinafter 'Keegan').

Hunt discloses a polynucleotide encoding (a nucleic acid (polynucleotide) encoding: abstract, paragraph [0030]) a fusion protein, wherein the fusion protein comprises a heterologous signal peptide and an MDA-7/IL-24 protein (a fusion protein, wherein the fusion protein comprises a heterologous signal peptide and an MDA-7/IL-24 protein; paragraph [0233]); a fusion protein encoded by the polynucleotide (a fusion protein encoded by the polynucleotide; paragraphs [0030, [0233]); a vector comprising the polynucleotide (a vector comprising the polynucleotide; abstract, paragraph [0030]); a method of treating cancer, the method comprising administering to a subject in need thereof the polynucleotide (a method of treating cancer, the method comprising administering to a subject in need thereof the polynucleotide; paragraphs [0028], [0030]).

Hunt does not disclose wherein the fusion protein comprises an insulin signal peptide and an MDA-7/IL-24 protein.

Keegan discloses expression constructs for delivering an exogenous polypeptide to a host (expression constructs for delivering an exogenous polypeptide to a host; abstract), including introduction into a non-host recombinant cell encapsulated in a semi-permeable membrane (including introduction into a non-host recombinant cell encapsulated in a semi-permeable membrane; abstract); wherein the construct comprises a sequence encoding an insulin secretory signal (wherein the construct comprises a sequence encoding an insulin secretory signal; paragraph [0005]) for efficient secretion of the heterologous gene (for efficient secretion of the heterologous gene; paragraph [0004]).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Hunt to have used the expression system, including the insulin signal peptide, of Keegan, in order to better enable secretion of the MDA-7/IL-24 fusion polypeptide into a subject administered the encapsulated cells for the treatment of cancer.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Hunt and Keegan references, unity of invention is lacking.

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.: 1-2, 5-8, 12/1-2, 12/5-8, 13/12/1-2, 13/12/5-8, 14/12/1-2, 14/12/5-8, 15/14/12/1-2, 15/14/12/5-8, 16/15/14/12/1-2, 16/15/14/12/5-8, 17/15/14/12/1-2, 17/15/14/12/5-8, 18/17/15/14/12/1-2, 18/17/15/14/12/5-8, 27/1-2, 27/5-8, 28/27/1-2, 28/27/5-8, 29/28/27/1-2, 29/28/27/5-8, 30/27/1-2, 30/27/5-8, 31/30/27/1-2, 31/30/27/5-8, 32/27/1-2, 32/27/5-8, 33/27/1-2, 33/27/5-8, 35-36, 39-42; SEQ ID Nos.: 5-7