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(54) Title: METHOD OF TREATMENT WITH VIRAL-BASED GENE THERAPY

(57) Abstract: Methods are provided for treating a patient with viral-based gene therapy that promote persistent transgene expression. The methods include administering to the patient an inhibitor of the interleukin-6 (IL6) signaling pathway or the NCOR2/SMRT histone deacetylation pathway, and a viral-based gene therapy vector. Methods are also provided for assigning viral-based gene therapy to a patient that include determining whether the patient has a genotype sensitizing the patient to persistent infection by a viral-based gene therapy vector by evaluating whether the patient has a mutation in the SMRT/NCOR2 gene associated with reduced SMRT/NCOR2 protein function or in the interleukin-6 receptor (IL-6R) gene associated with reduced IL-6R function. If the patient has either a mutation in the SMRT/NCOR2 gene associated with reduced SMRT/NCOR2 protein function or a mutation in the IL-6R gene associated with reduced IL-6R function, a viral-based gene therapy vector is assigned to the patient.



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INTERNATIONAL SEARCH REPORT

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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.:
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 additional 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 an 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.:

1-9, 33-35(completely); 16-32(partially)

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
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K48/00 A61P7/00 C12N15/86 C12N15/864
ADD.
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)
A61K A61P C07K C12N

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Victoria M Velasquez ET AL: "Effective Depletion of Pre-existing Anti-AAV Antibodies Requires Broad Immune Targeting.", Mol Ther Methods Clin Dev, 25 January 2017 (2017-01-25), pages 159-168, XP055509260, DOI: 10.1016/j.omtm.2017.01.003 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5363314/pdf/main.pdf [retrieved on 2018-09-24] abstract p. 160 col. 1, 2nd , p. 160 col. 2, 2nd , p. 160 col. 2, 2nd , p. 161 col. 2, last ----- -/--	1,3,4, 7-9, 16-21, 23-35

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

"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 30 November 2020	Date of mailing of the international search report 03/02/2021
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Landré, Julien
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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.
X	WO 2016/055437 A1 (ARTHROGEN B V [NL]) 14 April 2016 (2016-04-14) p. 1 li. 4-6, p. 22 li. 5-8, p. 2 li. 28-32, p. 24 li. 8-9, p. 24 li. 1-17, p. 2 li. 6-7, p. 24 li. 20-29, p. 1 li. 10-12, p. 23 li. 22-23, p.16 li. 26-28, p. 16 li. 30-31; claims 1, 5	1-9, 16-35
X	WO 02/09770 A1 (GENZYME CORP [US]) 7 February 2002 (2002-02-07) p. 2 li. 4-8, p. 7 li. 6-10, p. 10 li. 11-p. 12 li. 18, p. 2 li. 34-p. 3 li. 2, p. 6, li. 11-p. 7 li. 3, p. 3 li. 22-23; claims 1, 6, 7, 12	1,3,4, 7-9, 16-21,23
X	US 2018/193482 A1 (ILYINSKII PETR [US] ET AL) 12 July 2018 (2018-07-12) [0002]-[0003], [0025]-[0026], [0042], [0089], [0157]-[0158], [0065], [0067]-[0068], [0114], [0116]	1,3,4, 7-9, 16-21,23
X	WO 2016/168728 A2 (UNIV EMORY [US]; CHILDREN'S HEALTHCARE OF ATLANTA INC [US]) 20 October 2016 (2016-10-20) p. 3, li. 13-19, p. 4 li. 5-12, p. 35 li. 4-7, p. 50 li. 21-26, p. 51 clauses 17-18, p. 6, 8-21, p. 26 li. 28-35, p. 35 li. 11-14, p. 36 li. 9-11, p. 32 li. 33-34, p. 32 li. 5; claims 34, 37-38	1,3,4, 7-9, 16-21,23
X	SUSHRUSHA NAYAK ET AL: "Prevention and Reversal of Antibody Responses Against Factor IX in Gene Therapy for Hemophilia B", FRONTIERS IN MICROBIOLOGY, vol. 2, 1 January 2011 (2011-01-01), XP055730478, Lausanne ISSN: 1664-302X, DOI: 10.3389/fmicb.2011.00244 abstract; figures 1-2 p. 3, last ; p. 8 col. 1, last -p. 8 col. 2, last , p. 1, col. 2, last , p. 3, col. 1, 2nd -3rd , p. 4, col. 1, 1st , p. 7, col. 2, 1st , p. 9 col. 1, 2nd , p. 9 col. 1, last	1,3,4, 7-9, 16-21,23
A	WO 2017/083764 A1 (BAXALTA INC [US]; BAXALTA GMBH [CH]) 18 May 2017 (2017-05-18) the whole document	1-9, 16-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 33-35(completely); 16-32(partially)

A method for treating a patient with gene therapy using an IL-6 pathway inhibitor and a viral vector.

2. claims: 10-15(completely); 16-32(partially)

A method for treating a patient with gene therapy using an NCOR2/SMRT pathway inhibitor and a viral vector.

3. claims: 37, 41, 42, 46(completely); 36, 39, 43, 45(partially)

A method for treating a patient with gene therapy comprising determining a mutation in the IL-6R and administering a gene therapy.

4. claims: 38, 40, 44, 47(completely); 36, 39, 43, 45(partially)

A method for treating a patient with gene therapy comprising determining a mutation in the NCOR2/SMRT gene or IL-6R and administering a gene therapy.
