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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:**

3 December 2009

(54) **Title:** MODULATION OF ADENOVIRAL TROPISM

(57) **Abstract:** The invention provides materials and methods for modulating adenoviral tropism for hepatocytes and other cell types such as splenocytes. It relates to the findings that hypervariable regions (HVRs) of the viral hexon protein interact with the Gla domain of the blood clotting factor FX as part of the infective process in vivo. The invention provides means to disrupt the interaction between hexon and FX, thus reducing infection of hepatocytes and splenocytes, as well as use of targeting agents comprising the Gla domain or a fragment thereof to direct adenoviral vectors to desired target cell or tissue types.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/16 A61K35/58 C07K16/06 A61K48/00 G01N33/569
G01N33/68 A61K38/48 C12N15/861

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 C07K C12N G01N

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 practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, COMPENDEX, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PARKER ALAN L ET AL: "Multiple vitamin K-dependent coagulation zymogens promote adenovirus-mediated gene delivery to hepatocytes" BLOOD, vol. 108, no. 8, October 2006 (2006-10), pages 2554-2561, XP002537365 ISSN: 0006-4971 cited in the application page 2556, column 1, paragraph 3 - column 2, paragraph 1 page 2557, column 1, paragraph 2 - page 2558, column 1, paragraph 1; figure 4 ----- -/--	1-19

☒ 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 document 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

28 July 2009

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Name and mailing address of the ISA/

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International application No

PCT/GB2009/000363

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PARKER ALAN L ET AL: "Influence of coagulation factor zymogens on the infectivity of adenoviruses pseudotyped with fibers from subgroup D" JOURNAL OF VIROLOGY, vol. 81, no. 7, April 2007 (2007-04), pages 3627-3631, XP002537366 ISSN: 0022-538X Abstract page 3630, column 1	1-19
Y	THIEC F ET AL: "Role of the Gla and first epidermal growth factor-like domains of factor X in the prothrombinase and tissue factor-factor VIIa complexes" JOURNAL OF BIOLOGICAL CHEMISTRY 20030321 AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY INC. US, vol. 278, no. 12, 21 March 2003 (2003-03-21), pages 10393-10399, XP002537367 abstract	1-19
Y	RAHMAN A ET AL: "Specific depletion of human anti-adenovirus antibodies facilitates transduction in an in vivo model for systemic gene therapy" MOLECULAR THERAPY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 3, no. 5, 1 May 2001 (2001-05-01), pages 768-778, XP002977532 ISSN: 1525-0016 abstract	1-19
Y	KURACHI S ET AL: "Characterization of capsid-modified adenovirus vectors containing heterologous peptides in the fiber knob, protein IX, or hexon" GENE THERAPY, vol. 14, no. 3, February 2007 (2007-02), pages 266-274, XP002537368 ISSN: 0969-7128 abstract; figures	1-19
P,X	WADDINGTON SIMON N ET AL: "Adenovirus serotype 5 hexon mediates liver gene transfer" CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 132, no. 3, 8 February 2008 (2008-02-08), pages 397-409, XP009118580 ISSN: 0092-8674 cited in the application the whole document	1-19

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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.
P,Y	VIGANT FRÉDÉRIC ET AL: "Substitution of hexon hypervariable region 5 of adenovirus serotype 5 abrogates blood factor binding and limits gene transfer to liver." MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY AUG 2008, vol. 16, no. 8, August 2008 (2008-08), pages 1474-1480, XP009120092 ISSN: 1525-0024 abstract	1-19
Y	WO 99/36545 A (GENZYME CORP [US]; ROMANCZUK HELEN [US]; ARMENTANO DONNA [US]; RIORDAN) 22 July 1999 (1999-07-22) claims; examples	1-19

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 allsearchable 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 reportcovers 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.:

see add. sheet

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-19

Method, use, agent, pharmaceutical preparation and kit for inhibiting the interaction between FX and adenoviral hexon protein and an adenovirus

2. claims: 20-36

Method, targeting agent, use, pharmaceutical preparation and kit for gene delivery using a fragment of FX Gla domain associated with a binding agent for target cell

3. claims: 37-47

Method of screening for an agent for modulating hepatocyte transduction

4. claims: 48-77

Method of screening for an adenoviral hexon protein having altered affinity for FX or for an adenovirus having altered ability to transduce hepatocytes or splenocytes

5. claims: 78-100

Method, protein, DNA/vector/cell for modified hepatocyte transduction

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2009/000363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9936545	A	22-07-1999	
		AU 2321999 A	02-08-1999
		CA 2317941 A1	22-07-1999
		EP 1044274 A2	18-10-2000
		JP 2002508967 T	26-03-2002