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- 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))

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(54) Title: POTENTIATION OF AUTOIMMUNE AND INFLAMMATORY DISEASE TREATMENTS BY IMMUNE REGULATORY OLIGONUCLEOTIDE (IRO) ANTAGONISTS OF TLR7 AND TLR9

(57) Abstract: The invention provides the use of immune regulatory oligonucleotides (IRO) as antagonist of TLRs and potentiators of anti-inflammatory agents that inhibit TNF for the prevention and treatment of inflammatory and autoimmune diseases.



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INTERNATIONAL SEARCH REPORT

International application No

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/117

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)

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 practical, search terms used)

EPO-Internal, BIOSIS, Sequence Search, 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	WO 2005/072290 A2 (JOSLIN DIABETES CENTER INC [US]; MATHIS DIANE J [US]; BENOIST CHRISTOP) 11 August 2005 (2005-08-11) page 18, line 16 - line 17; claims 1,6,20,21 -----	1-12
X	WO 2007/038720 A2 (COLEY PHARM GMBH [DE]; COLEY PHARM GROUP INC [US]; JURK MARION [DE]; V) 5 April 2007 (2007-04-05) page 12 - page 17 page 37 - page 38; claims 1,25-27,30, -----	1-12
A	US 2004/097719 A1 (AGRAWAL SUDHIR [US] ET AL) 20 May 2004 (2004-05-20) ----- -/-	11,12

☒ 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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/036923

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	L. AURISICCHIO ET AL: "Treatment of Mammary Carcinomas in HER-2 Transgenic Mice through Combination of Genetic Vaccine and an Agonist of Toll-Like Receptor 9", CLINICAL CANCER RESEARCH, vol. 15, no. 5, 17 February 2009 (2009-02-17), pages 1575-1584, XP55014631, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-08-2628 -----	1-12
A	H. WANG ET AL: "Immunomodulatory oligonucleotides as novel therapy for breast cancer: pharmacokinetics, in vitro and in vivo anticancer activity, and potentiation of antibody therapy", MOLECULAR CANCER THERAPEUTICS, vol. 5, no. 8, 1 August 2006 (2006-08-01), pages 2106-2114, XP55014635, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-06-0158 -----	1-12
A	V. DAMIANO ET AL: "TLR9 agonist acts by different mechanisms synergizing with bevacizumab in sensitive and cetuximab-resistant colon cancer xenografts", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 104, no. 30, 24 July 2007 (2007-07-24), pages 12468-12473, XP55014634, ISSN: 0027-8424, DOI: 10.1073/pnas.0705226104 -----	1-12
A	AGRAWAL SUDHIR ET AL: "Medicinal chemistry and therapeutic potential of CpG DNA", TRENDS IN MOLECULAR MEDICINE, ELSEVIER CURRENT TRENDS, GB, vol. 8, no. 3, 1 March 2002 (2002-03-01), pages 114-121, XP009073678, ISSN: 1471-4914, DOI: 10.1016/S1471-4914(01)02264-X ----- -/--	1-12

INTERNATIONAL SEARCH REPORT

International application No.
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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.: 1-12(partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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:

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.:

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/US2010/036923

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TAMARA LOOS ET AL: "TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis", LABORATORY INVESTIGATION, vol. 86, no. 9, 1 September 2006 (2006-09-01), pages 902-916, XP55014656, ISSN: 0023-6837, DOI: 10.1038/labinvest.3700453 -----	1-12
A	JOSHUA R. KORZENIK ET AL: "Evolving knowledge and therapy of inflammatory bowel disease", NATURE REVIEWS DRUG DISCOVERY, vol. 5, no. 3, 1 March 2006 (2006-03-01), pages 197-209, XP55014668, ISSN: 1474-1776, DOI: 10.1038/nrd1986 -----	1-12
A	Idera Pharmaceuticals: "Idera Pharmaceuticals to Present Preclinical Data on its Agonists of Toll-Like Receptors at AACR 2009 Annual Meeting", 15 April 2009 (2009-04-15), XP002666052, Retrieved from the Internet: URL:http://ir.iderapharma.com/phoenix.zhtm l?c=208904&p=irol-newsArticle&ID=1276520&highlight= [retrieved on 2011-12-14] -----	1-12
A	Idera Pharmaceuticals: "Idera Pharmaceuticals Announces Presentation of Preclinical Data on IMO-3100, a Lead TLR Antagonist Drug Candidate for Autoimmune Diseases, during American Association of Immunologists Annual Meeting", 11 May 2009 (2009-05-11), XP002666053, Retrieved from the Internet: URL:http://ir.iderapharma.com/phoenix.zhtm l?c=208904&p=irol-newsArticle&ID=1286667&highlight= [retrieved on 2011-12-19] ----- -/--	1-12

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/036923

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Gu-Gang Zhu ET AL: "Studies of Combination of IMO-3100, an Antagonist of TLR7 and TLR9, and Etanercept, a TNF-alpha Inhibitor, in a Mouse Model of Collagen-Induced Arthritis (CIA)", Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals, 19 October 2009 (2009-10-19), XP55014802, Philadelphia, PA, USA Retrieved from the Internet: URL: http://www.iderapharma.com/development/IMO-3100_Pres-4%28poster%29.pdf [retrieved on 2011-12-14] -----	1-10
X,P	idera Pharmaceuticals: "Idera Pharmaceuticals Presents Preclinical Data at ACR/ARHP 2009 Annual Meeting on IMO-3100, a Toll-Like Receptor Antagonist, in Combination with Enbrel(R) in Arthritis Model", 19 October 2009 (2009-10-19), XP002666054, Retrieved from the Internet: URL: http://ir.iderapharma.com/phoenix.zhtml?c=208904&p=irol-newsArticle&ID=1343342&highlight= [retrieved on 2011-12-14] -----	1-10
X,P	EP 2 154 144 A1 (CHANGCHUN HUAPU BIOTECHNOLOGY [CN]) 17 February 2010 (2010-02-17) the whole document -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/036923

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005072290 A2	11-08-2005	US 2008020991 A1 WO 2005072290 A2	24-01-2008 11-08-2005
WO 2007038720 A2	05-04-2007	AU 2006294528 A1 BR PI0616770 A2 CA 2623764 A1 CN 101340931 A EA 200800943 A1 EP 1928500 A2 JP 2009510096 A KR 20080059595 A WO 2007038720 A2	05-04-2007 28-06-2011 05-04-2007 07-01-2009 30-12-2008 11-06-2008 12-03-2009 30-06-2008 05-04-2007
US 2004097719 A1	20-05-2004	NONE	
EP 2154144 A1	17-02-2010	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-12(partially)

Present claims 1-12 relate to methods using compounds which have a given desired property or effect, namely "IRO" (Immune Regulatory Oligonucleotide) and "anti-inflammatory agent that inhibits TNF". However, the description does not provide support and disclosure in the sense of Article 6 and 5 PCT for all compounds having the said property or effect and there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9.19 and 9.20). The search of claims 1-12 was consequently restricted to methods using the specifically disclosed compounds having the desired property or effect, namely unmethylated CpG oligonucleotides which act as TLR7 and TLR9 antagonists, and known TNF-alpha inhibitors such as soluble TNF-alpha receptor fusion proteins (e.g. etanercept) and anti-TNF-alpha antibodies (e.g. infliximab or adalimumab)(see claims 4, 11 and 12 and description page 15, paragraph [0069] and Examples 1 and 2).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.