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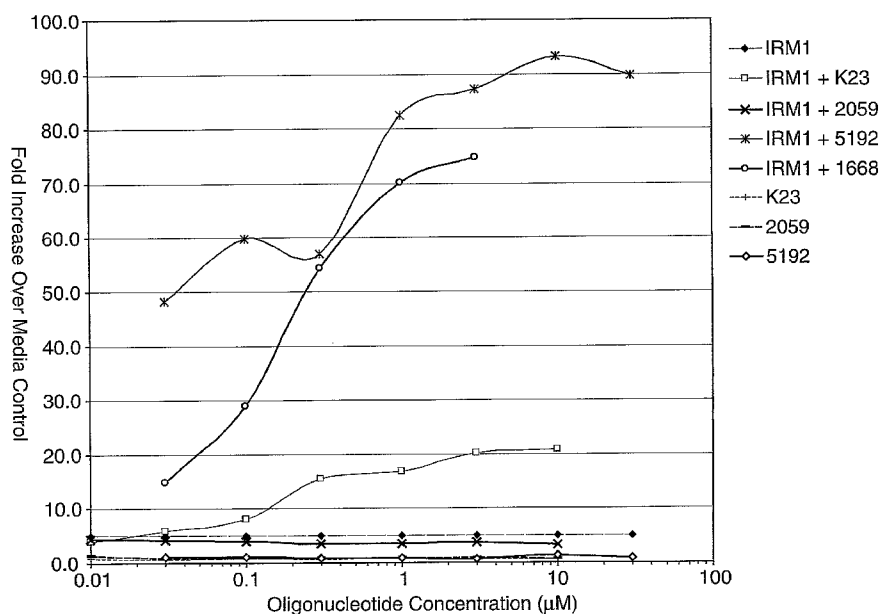
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[Continued on next page]

(54) Title: IMMUNOSTIMULATORY COMBINATIONS AND METHODS



(57) Abstract: The invention provides immunostimulatory combinations and methods of enhancing TLR8-mediated biological activity. Generally, the immunostimulatory combinations include a TLR8 agonist and an immunostimulatory oligonucleotide in an amount effective to enhance TLR8-mediated biological activity. The invention also provides methods of inducing TLR8-mediated biological activity in immune cells. Generally, the methods include contacting immune cells with an immunostimulatory combination that includes a TLR8 agonist and an immunostimulatory oligonucleotide in an amount effective to enhance TLR8-mediated biological activity. In some cases, the immunostimulatory combination provides a synergistic enhancement of TLR8-mediated biological activity.

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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report*

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/44448

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: A01N 43/04(2006.01);A61K 31/70(2006.01)
 USPC: 514/44
 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)
 U.S. : 514/44

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)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0139364 A1 (KRIEG et al.) 24 July 2003 (24.07.2003) page 85 lines 7-24, page 1 paragraph 0014, page 40 paragraph 0414, page 43 paragraph 0445.	1-9, 12-16 10, 11
Y	US 2004/0141950 A1 (NOELLE et al.) 22 July 2004(22.07.2004) page 12 Column 1.	10, 11
A	US 2004/0162309 A1 (GORDEN et al.) 19 August 2004.	1-9, 12-16 1-16
A	US 2003/0232074 A1 (LIPFORD et al.) 18 December 2003.	1-16

<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input type="checkbox"/> See patent family annex.
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"Z" document member of the same patent family</p>

Date of the actual completion of the international search
 10 August 2006 (10.08.2006)

Date of mailing of the international search report
 02 OCT 2006

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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	US2005/0171072 A1 (TOMAI et al.) 04 August 2005.	1-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/44448

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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-16
- 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/US05/44448

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-16, drawn to an immunostimulatory combination comprising a TLR8 agonist and an immunostimulatory oligonucleotide.

Group II, claim(s) 17-39, drawn to a method of inducing TLR8-mediated biological activity in immune cells.

The inventions listed as Groups I and II 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:

The technical feature of Group I is the immunostimulatory combination comprising a TLR8 agonist and an immunostimulatory oligonucleotide. This technical feature is anticipated by Krieg et al (US patent application publication No.: US 2003/0139364 A1).

Continuation of B. FIELDS SEARCHED Item 3:

PUBMED, WEST, DIALOG (EMBASE, MEDLINE)

Search terms: toll receptor , toll like receptor , TLR8, imidazoquinoline amine, imidazoquinoline, oligonucleotide, oligodinucleotide, immunostimulatory oligonucleotide, CpG