

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 November 2009 (26.11.2009)

PCT

(10) International Publication Number
WO 2009/143390 A3

- (51) **International Patent Classification:**
C12Q 1/68 (2006.01) *C07H 21/04* (2006.01)
- (21) **International Application Number:**
PCT/US2009/044919
- (22) **International Filing Date:**
21 May 2009 (21.05.2009)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/128,628 22 May 2008 (22.05.2008) US
- (71) **Applicant (for all designated States except US):** **ISIS PHARMACEUTICALS, INC.** [US/US]; 1896 Rutherford Road, Carlsbad, CA 92008 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **MONIA, Brett, P.** [US/US]; 2306 Casa Hermosa Court, Encinitas, CA 92024 (US). **YU, Xing-Xian** [US/US]; 12605 El Camino Real, Unit F, San Diego, CA 92130 (US). **BHANOT, Sanjay** [US/US]; 8094 Paseo Arrayan, Carlsbad, CA 92009 (US).
- (74) **Agents:** **SPAIN, Astrid, R.** et al.; McDermott Will & Emery LLP, Torrey Reserve - North Court, 11682 El Camino Real, Suite #400, San Diego, CA 92130 (US).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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))
- with sequence listing part of description (Rule 5.2(a))

(88) **Date of publication of the international search report:**
14 January 2010



WO 2009/143390 A3

(54) **Title:** METHODS FOR MODULATING EXPRESSION OF RBP4

(57) **Abstract:** Methods are provided for modulating RBP4 by administering a RBP4-specific modulator. Also provided are methods for treating cardiovascular and metabolic disorders in a subject or delaying or preventing risk factors thereof through the modulation of RBP4. The present invention is also directed to methods of decreasing lipid levels in a subject or for preventing or delaying the onset of a rise in lipid levels in a subject, comprising administering to said subject a RBP4-specific inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/44919

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12Q 1/68; C07H 21/04 (2009.04) USPC - 435/6; 536/24.5 According to International Patent Classification (IPC) or to both national classification and IPC</p>											
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC(8) - C12Q 1/68; C07H 21/04 (2009.04) USPC - 435/6; 536/24.5</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST (PGPB,USPT,USOC,EPAB,JPAB); Google Scholar: RBP, RBP4, PRBP, retinol-binding protein 4, retinol binding protein 4, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, hyperfattyacidemia, hypertriglyceridaemia, hyperglyceridemia, diabetes, obesity, fat, fatty</p>											
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:10%;">Category*</th> <th style="width:70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width:20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X ----- Y</td> <td>US 2005/0208535 A1 (KAHN et al.) 22 Sep 2005 (22.09.2005) para [0004]-[0005], [0009], [0012], [0015], [0108], [0116], [0120]-[0121], [0130]</td> <td>1-4, 7, 12 ----- 5-6</td> </tr> <tr> <td>Y</td> <td>US 2004/0053367 A1 (GRIFFIN et al.) 18 Mar 2004 (18.03.2004) para [0217]-[0218]</td> <td>5-6</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X ----- Y	US 2005/0208535 A1 (KAHN et al.) 22 Sep 2005 (22.09.2005) para [0004]-[0005], [0009], [0012], [0015], [0108], [0116], [0120]-[0121], [0130]	1-4, 7, 12 ----- 5-6	Y	US 2004/0053367 A1 (GRIFFIN et al.) 18 Mar 2004 (18.03.2004) para [0217]-[0218]	5-6
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.									
X ----- Y	US 2005/0208535 A1 (KAHN et al.) 22 Sep 2005 (22.09.2005) para [0004]-[0005], [0009], [0012], [0015], [0108], [0116], [0120]-[0121], [0130]	1-4, 7, 12 ----- 5-6									
Y	US 2004/0053367 A1 (GRIFFIN et al.) 18 Mar 2004 (18.03.2004) para [0217]-[0218]	5-6									
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>											
<p>* Special categories of cited documents:</p> <table style="width:100%;"> <tr> <td style="width:50%;"> <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 but 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> </td> <td style="width:50%;"> <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>"&" document member of the same patent family</p> </td> </tr> </table>			<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 but 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>"&" document member of the same patent family</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 but 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>"&" document member of the same patent family</p>										
<p>Date of the actual completion of the international search</p> <p>12 August 2009 (12.08.2009)</p>		<p>Date of mailing of the international search report</p> <p align="center">24 AUG 2009</p>									
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201</p>		<p>Authorized officer:</p> <p align="right">Lee W. Young</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>									

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/44919

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.: 8-11 and 13-54
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 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.