



- (51) **International Patent Classification:**
C12N 15/11 (2006.01) *A61K 31/7088* (2006.01)
- (21) **International Application Number:**
PCT/US2012/035648
- (22) **International Filing Date:**
27 April 2012 (27.04.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/479,815 27 April 2011 (27.04.2011) US
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- (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, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, SE, SI, SK, SM, 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:**
27 December 2012

(54) **Title:** MODULATION OF CD36 EXPRESSION

(57) **Abstract:** Provided herein are methods, compounds, and compositions for reducing expression of a CD36 mRNA and protein in an animal. Also provided herein are methods, compounds, and compositions for reducing lipids and atherosclerotic plaques in an animal. Such methods, compounds, and compositions are useful to treat, prevent, delay, or ameliorate any one or more of cardiovascular disease or inflammatory disease, or a symptom thereof.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/35648

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 15/11, A61K 31/7088 (2012.01)
USPC - 514/44A

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)
USPC -- 514/44A

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)
PubWEST -- PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files -- 654, 652, 349, 348, 340, 35, 65, 155; USPTO Web Page; Google Scholar; Search terms -- CD36 inhibition, sequence, modified oligonucleotide, bicyclic sugar, 2'-methoxyethyl, wing, gap, 5-methylcytosine, plaque reduction, statins, niacin, triglyceride level, LDL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2004/0077567 A1 (WATT et al.) 22 April 2004 (22.04.2004) para [0013], [0016], [0017], [0024], [0026], [0029], [0033], [0034], [0041], [0042], [0057], [0201], [0228], [0241], [0245]-[0247]	1, 8-22, 31-34, 41 ----- 5, 26-30, 35-40, 42
Y	US 2010/0105088 A1 (HANDBERG et al.) 29 April 2010 (29.04.2010) para [0005], [0131], [0184], [0186], [0218], abstract	5, 36-40, 42
Y	US 6,322,976 B1 (AITMAN et al.) 27 November 2001 (27.11.2001) col 9, ln 41-44; col 30, ln 56 -- col 31, ln 25; col 61, ln 34-62; col 85, ln 5-10	26-30, 35-40

☐ Further documents are listed in the continuation of Box C. ☐

* 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

16 September 2012 (16.09.2012)

Date of mailing of the international search report

16 OCT 2012

Name and mailing address of the ISA/US

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P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/35648

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:

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: claims 1, 5, 8-22, and 26-42, directed to a method of reducing CD36 expression in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein expression of CD36 is reduced in the animal.

Group II: claims 2, 8-22, and 31-42, directed to a method of reducing LDL-C levels in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein expression of LDL-C is reduced in the animal.

- Please see extra sheet for continuation -

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.:
1, 5, 8-22 and 26-42

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/US 12/35648

Continuation of Box III: Lack of Unity of Invention

Group III: claims 3, 8-22, and 31-42, directed to a method of reducing triglyceride levels in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein the level of triglyceride is reduced in the animal.

Group IV: claims 4, 8-22, and 31-42, directed to a method of reducing cholesterol levels in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein the level of cholesterol is reduced in the animal

Group V: claims 6, 8-22, and 31-42, directed to a method of reducing one or more of atherosclerotic plaque numbers or size in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein one or more of the number or size of the atherosclerotic plaque is reduced in the animal.

Group VI: claims 7-25, and 30-42, directed to a method of treating, preventing or ameliorating an inflammatory or cardiovascular disease in an animal comprising administering to the animal a compound comprising a modified oligonucleotide 10 to 30 linked nucleosides in length targeted to CD36, wherein the inflammatory or cardiovascular disease is treated, prevented or ameliorated in the animal.

Group VII: claims 43-56, directed to a compound comprising a modified oligonucleotide consisting of 10 to 30 linked nucleosides targeting CD36 as shown in any of SEQ ID NOs: 1-8.

Group VIII: claim 57, directed to use of a compound targeting CD36 for treating, preventing, ameliorating or reducing at least one symptom of an inflammatory or cardiovascular disease, by decreasing CD36.

Group IX: claim 58, directed to use of a compound targeting CD36 for treating, preventing, ameliorating or reducing atherosclerosis by decreasing CD36.

The inventions listed as Groups I - IX 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 special technical features of the claims of Groups I-IX are disclosed in the Group descriptions, above.

There is no common technical element shared by all of the above groups. Groups I-VII share the common technical element of being related to modified oligonucleotides consisting of 10 to 30 linked nucleosides targeting CD36. Groups VIII and IX share the common technical element of being related to the use of compounds targeting CD36 for treating, preventing, ameliorating, or reducing at least one symptom of a disease or condition by decreasing CD36. Groups I-VII also share the common technical element of being related to any of SEQ ID NOs: 1-8. Groups V and IX share the common technical element of being related to atherosclerosis. Groups VI and VIII share the common technical element of being related to an inflammatory or cardiovascular disease. These common technical elements do not represent an improvement over the prior art of US 2004/0077567 A1 to Watt et al., which teaches antisense compounds, compositions and methods for modulating the expression of CD36, targeted to nucleic acids encoding CD36, for the treatment of diseases associated with expression of CD36 (abstract), wherein the oligonucleotides comprise 10-30 nucleosides (claim 1), and may be modified (para [0030]). Watt further teaches wherein the administration may be for treatment of atherosclerosis (para [0013]), or inflammatory conditions (para [0055]). Furthermore, Watt teaches wherein at least one sequence targeted comprises any of SEQ ID NOs: 1-8, particularly SEQ ID NO: 3 (Watt's SEQ ID NO: 3 is identical to applicants' SEQ ID NO: 3).

Therefore, the inventions of Groups I-IX lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.