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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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) **Date of publication of the international search report**:
6 December 2012

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(54) **Title**: MODULATION OF SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3) EXPRESSION

(57) **Abstract**: Disclosed herein are antisense compounds and methods for decreasing STAT3 mRNA and protein expression. Such methods, compounds, and compositions are useful to treat, prevent, or ameliorate hyperproliferative diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/31642

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07H 21/04; C12N 15/11 (2012.01)
USPC - 536/24.5; 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: 536/24.5; 514/44A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 536/24.5; 514/44A; 435/375 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PubWEST (USPT, EPAB, JPAB, PGPB); Google Scholar; GenCore sequence search (NT)
Search terms: STAT3, modified antisense oligonucleotide, substituted nucleoside, hyperproliferative disease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0054003 A1 (KARRAS) 3 March 2011 (11.03.2011). Especially para [0213], Table 1, pg 22 Table 2, SEQ ID NO: 15.	4, 29
X	US 2010/0298409 A1 (XIE et al.) 25 November 2010 (25.11.2010)	1, 2, 6, 27, 46, 48
A	NCBI REFERENCE SEQUENCE NM_ 139276.2. Homo sapiens signal transducer and activator of transcription 3 (acute-phase response factor) (STAT3), transcript variant 1, mRNA. [online] 27 March 2011 [retrieved 5 September 2012]. Available on the internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/47080104?sat=14&satkey=6009123>. Especiallly pg 6-7.	1, 2, 4, 6, 7, 27, 29, 46, 48
A	GENBANK L29277.1. Homo sapiens DNA-binding protein (APRF) mRNA, complete cds. [online] 31 December 1994 [retrieved 5 September 2012]. Available on the internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/L29277>. Especially pg 1-2.	1, 2, 4, 6, 7, 27, 29, 46, 48

☐ 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	Date of mailing of the international search report
10 September 2012 (10.09.2012)	21 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/31642

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.: 10-26, 30-45 and 49-65
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, 2, 4, 6, 7, 27, 29 (limited to those sequences having the characteristics described herein for Group I), 46, and 48, directed to a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of SEQ ID NO: 1, or subsequences thereof.

Group II: claims 3, 5, 8, 9, and 28, 29 (limited to those sequences having the characteristics described herein for Group II), 47, and 48, directed to a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides having a nucleobase sequence comprising a portion of at least 12 contiguous nucleobases complementary to an equal length portion of SEQ ID NO: 2.

----------for continuation, go to Extra 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 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, 2, 4, 6, 7, 27, 29, 46, and 48 limited to SEQ ID NO: 1 and any of its subsequences

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 12/31642

Continuation of Box III (Lack of Unity of Invention)

Groups III+: claims 66-73, directed to a method of treating a hyperproliferative disease in an animal, comprising administering to an animal in need thereof a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 9-426, 430-442, 445-464, 471-498,500-1034, 1036-1512, and 1541-2757; wherein the first invention is limited to SEQ ID NO: 9 (claims 66 and 69-73) (applicants may opt for additional sequences to be searched by specifying the SEQ ID NO: and paying an additional invention search fee for each elected sequence).

Groups IV+: claims 74-76, directed to a method of reducing expression of STAT3 in an animal, comprising administering to an animal in need thereof a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 9-426, 430-442, 445-464, 471-498, 500-1034 and 1036-1512; wherein the first invention is limited to SEQ ID NO: 9 (claim 74) (applicants may opt for additional sequences to be searched by specifying the SEQ ID NO: and paying an additional invention search fee for each elected sequence).

The inventions listed as Groups I, II, III+ and IV+ 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, II, III+ and IV+ are indicated above in the Group descriptions.

The only common technical element shared by the above groups is that they are related to STAT3, and nucleic acid sequences associated therewith. The subgroups of Groups III+ and IV+ share the common technical elements of being related to administering to an animal in need thereof a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 9-426, 430-442, 445-464, 471-498, 500-1034 and 1036-1512, wherein, for Groups III+, the administration is associated with a method of treating a hyperproliferative disease in an animal; while administration in Groups IV+ is associated with reducing STAT3 expression. These common technical elements do not represent an improvement over the prior art of US 2011/0054003 A1 to Karras et al., which teaches a method of treating a hyperproliferative disease in an animal ("Effect of STAT3 Antisense Oligonucleotides on Leukemic Large Granular Lymphocytes (LGL)"; para [0256] "LGL leukemia is a lymphoproliferative disease with autoimmune features and LGL cells are known to be insensitive to Fas-dependent cell death despite high levels of Fas and FasL expression. STAT3 antisense oligonucleotides were tested for their ability to sensitize LGL cells to the apoptotic signal in these cells"; para [0257] "Cells were incubated with either ISIS 17148 antisense oligonucleotide (SEQ ID NO: 95) or the control, ISIS 16094 (SEQ ID NO: 152). Antisense oligonucleotide delivery to LGL leukemic cells was by passive uptake and no transfection reagents were included in the reaction"), comprising administering to an animal in need thereof a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of SEQ ID NO: 212 (para [0258]; "Both ISIS 17148 and ISIS 16094 are 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings." The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All 2'-MOE cytosines and 2'-deoxy cytosines were 5-methyl-cytosines"; para [0259]; "Extracts of LGL cells treated with antisense oligonucleotides (1 uM dosing for ISIS 17148 and the control) from three patients were obtained and assayed for STAT3 protein levels by Western blot. Sensitization of the LGL cells to Fas-mediated apoptosis was also measured by flow cytometry in cells treated with antisense oligonucleotides at doses of 1, 2 and 5 uM. By Western analysis, a reduction in STAT3 protein levels ranged from 25 to 45%. Sensitivity to Fas mediated apoptosis was also significantly increased in the antisense treated cells and was dose dependent. Measurements of percent specific apoptosis in duplicate reactions revealed an increase in apoptosis from 5% in untreated cells to levels of 6, 17 and 24% in antisense-treated cells at 1, 2, and 5 .mu.M, respectively. Levels of apoptosis in control oligonucleotide treated cells remained at 6% at all doses"; pg 25 Table 3: Summary of ISIS 17148 (SEQ ID NO: 95) as 20 nucleotide antisense sequence ACTCAAACTGCCCTCCTGCT that targets STAT3 nt 2309-2328 of Mouse STAT 3 (coding region)" and comprises Applicants' SEQ ID NO: 212).
Therefore, the inventions of Groups I, II, III+ and IV+ lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

(It should be further noted that, should the applicants elect both to pay for searches of additional inventions, such as any of the inventions of Groups II, III+ or IV+, and pay for the search of additional sequences in said groups, the Applicants will not be required to pay for the additional search of the same sequence in different Groups for which payment has been made. All elected sequences for which a search payment has been made will be searched in all Groups for which a search payment has been made).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/31642

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.4.1