(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2012 (13.12.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/170945 A3

(51) International Patent Classification:
A61K 48/00 (2006.01) *C07H 21/04* (2006.01)

(21) International Application Number:
PCT/US2012/041743

(22) International Filing Date:
8 June 2012 (08.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/495,945 10 June 2011 (10.06.2011) US
61/496,462 13 June 2011 (13.06.2011) US

(71) Applicant *(for all designated States except US)*: **ISIS PHARMACEUTICALS, INC.** [US/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BHATTACHARJEE, Gourab** [US/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US). **REVENKO, Alexey** [RU/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US). **MACLEOD, Robert, A.** [CA/US]; 2855 Gazelle Court, Carlsbad, CA 92010 (US).

(74) Agents: **GINGRICH, Brenden** et al.; 2040 Main Street, 14th Floor, Irvine, CA 92614 (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, 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:
31 January 2013

WO 2012/170945 A3

(54) Title: METHODS FOR MODULATING KALLIKREIN (KLKB1) EXPRESSION

(57) Abstract: Disclosed herein are methods for decreasing kallikrein and treating or preventing inflammatory conditions in an individual in need thereof. Examples of disease conditions that can be ameliorated with the administration of antisense compounds targeted to kallikrein include hereditary angioedema (HAE). Methods for inhibiting kallikrein can also be used as a prophylactic treatment to prevent individuals at risk for developing an inflammatory condition, such as, hereditary angioedema.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41743

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 48/00; C07H 21/04 (2012.01)
USPC - 514/44R, 536/23.1
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)
IPC(8) - A61K 48/00; C07H 21/04 (2012.01)
USPC - 514/44R, 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/43, 42, 23, 1, 536/22.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar
Search terms: kallikrein, angioedema, angiooedema, hereditary, siRNA, shRNA, snoRNA, miRNA, antisense, silencing

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0191296 A1 (GOLZ et al.) 16 August 2007 (16.08.2007) para [0137], [0140], [0294], [0308], [0327]	1
X	US 2007/0253949 A1 (GOLZ et al.) 1 November 2007 (01.11.2007) para [0177], [0180], [0291], [0301], [0310], [0332]	1
Y	SCHNEIDER et al., Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. J Allergy Clin Immunol, August 2007, Vol 120, No 2, pages 416-22. Especially abstract; p 416, col 2, para 2; p 417, col 2, para 1-3	1
Y	US 2008/0280811 A1 (FEENER et al.) 13 November 2008 (13.11.2008) para [0014], [0062], [0076]-[0077]	1

☐ 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
30 October 2012 (30.10.2012)	20 NOV 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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41743

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.: 3-10, 18-35
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: Claim 1, drawn to methods for prophylactic treatment for an animal at risk for experiencing an attack of hereditary angioedema.

Group II: Claims 2, 11-13, 17, drawn to methods for prophylactic treatment for an animal at risk for or exhibiting an inflammatory condition, and methods for inhibiting inflammation.

Group III: Claim 14, drawn to a method for inhibiting edema.

Group IV: Claim 15, drawn to a method for inhibiting vascular permeability.

---please see 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

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 12/41743

Continuation of Box No III Observations where unity of invention is lacking

Group V: Claim 16, drawn to a method for inhibiting vascular leakage.

Group VI: Claims 36-38, drawn to a modified oligonucleotide complementary to kallikrein and use of a modified oligonucleotide in the manufacture of a medicament.

Group VII: Claims 39-42, drawn to methods comprising increasing or stabilizing HMWK.

The inventions listed as Groups I-VII 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 shared technical feature of the inventions listed as Groups I-VII is a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is at least 90% complementary to a kallikrein nucleic acid. This shared technical feature fails to provide a contribution over the prior art, as evidenced by US 2008/0280811 A1 to Feener et al. (published November 13, 2008; hereinafter 'Feener'). Feener discloses a kallikrein inhibitor (para [0062] - "Suitable kallikrein/kinin signalling inhibitors can act at any point in the kallikrein/kinin pathway, and include, but are not limited to, inhibitory nucleic acids, e.g., antisense, RNAi, and aptamers, that are specific for a protein in the pathway") comprising a modified oligonucleotide (para [0077] - " an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides") consisting of 12 to 30 linked nucleosides (para [0076] - "An antisense oligonucleotide can be, for example, about 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or more nucleotides in length"), wherein the modified oligonucleotide is at least 90% complementary to a kallikrein nucleic acid (para [0076] - "An antisense nucleic acid can be designed such that it is complementary to the entire coding region of a target mRNA, but can also be an oligonucleotide that is antisense to only a portion of the coding or noncoding region of the target mRNA"). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Groups I-V is a method for treating an animal comprising administering to the animal a therapeutically effective amount of a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is at least 90% complementary to a kallikrein nucleic acid. This shared technical feature fails to provide a contribution over the prior art, as evidenced by the article entitled "Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor" by Schneider et al. (published in J Allergy Clin Immunol, August 2007, Vol 120, No 2, pages 416-22; hereinafter 'Schneider' in view of Feener. Schneider discloses a method comprising, identifying an animal at risk for experiencing an attack of hereditary angioedema (abstract - "Hereditary angioedema (HAE) is a rare, autosomal-dominant disorder caused by C1 inhibitor gene mutation. Patients with HAE experience intermittent attacks"; p 417, col 2, para 3 - "Patients were required to be at least 10 years of age and to have confirmed HAE. Diagnosis was established by the presence of at least 1 clinical and 1 laboratory criterion"); and administering to the at risk animal a therapeutically effective amount of an inhibitor of kallikrein (abstract - administration of ecallantide, an inhibitor of kallikrein; p 417, col 2, para 1 - "Patients were randomized to treatment with a single dose of ecallantide (5, 10, 20, or 40 mg/m2 intravenously) or placebo (PBS) by intravenous infusion"). Schneider does not specifically disclose that the administration is prophylactic. However, Schneider does teach that researchers have been searching for prophylactic medical treatments for hereditary angioedema (p 416, col 2, para 2), and one of ordinary skill in the art would have found it obvious that prophylactic administration would be beneficial since it would allow patients who have hereditary angioedema to avoid suffering through the uncomfortable symptoms of an attack. Further, Schneider does not disclose wherein the inhibitor of kallikrein is a modified oligonucleotide consisting of 12 to 30 linked nucleosides, wherein the modified oligonucleotide is at least 90% complementary to a kallikrein nucleic acid. However such kallikrein inhibitors are known in the art, as exemplified by Feener, which discloses a kallikrein inhibitor (para [0062] - "Suitable kallikrein/kinin signalling inhibitors can act at any point in the kallikrein/kinin pathway, and include, but are not limited to, inhibitory nucleic acids, e.g., antisense, RNAi, and aptamers, that are specific for a protein in the pathway") comprising a modified oligonucleotide (para [0077] - " an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides") consisting of 12 to 30 linked nucleosides (para [0076] - "An antisense oligonucleotide can be, for example, about 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or more nucleotides in length"), wherein the modified oligonucleotide is at least 90% complementary to a kallikrein nucleic acid (para [0076] - "An antisense nucleic acid can be designed such that it is complementary to the entire coding region of a target mRNA, but can also be an oligonucleotide that is antisense to only a portion of the coding or noncoding region of the target mRNA"). Feener further discloses the administration of the modified oligonucleotides to a subject (para [0014]). One of ordinary skill in the art would have found it obvious to modify the method of Schneider in view of the kallikrein inhibitor of Feener because Schneider teaches that inhibition of kallikrein was shown to be effective in treating hereditary angioedema, and Feener provides a composition that is capable of inhibiting kallikrein. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Groups II and VII is the treatment of an inflammatory condition. This shared technical feature fails to provide a contribution over Feener, which discloses treatment (para [0008] - "methods for the treatment of disorders associated with excessive vascular permeability") of an inflammatory condition (para [0018] - "Other disorders associated with increased permeability include, but are not limited to, excessive vascular permeability associated with hypertension or inflammation"). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature

Further, the special technical feature of the inventions listed as Group I is the treatment of hereditary angioedema. This special technical feature is not shared by the inventions of Groups II-VII. The special technical feature of the inventions listed as Group III is the inhibition of edema. This special technical feature is not shared by the inventions of Groups II-VII. The special technical feature of the inventions listed as Group IV is the inhibition of vascular permeability. This special technical feature is not shared by the inventions of Groups I-III and V-VII. The special technical feature of the inventions listed as Group V is the inhibition of vascular leakage. This special technical feature is not shared by the inventions of Groups I-IV and VI-VII. The special technical feature of the inventions listed as Group VII is the increase or stabilization of HMWK. This special technical feature is not shared by the inventions of Groups I.

The inventions of Groups I-VII lack the same or corresponding special technical features and therefore lack unity with one another.