4332

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
15 June 2006 (15.06.2006)

(10) International Publication Number
WO 2006/063128 A2

(51) International Patent Classification:
A61K 48/00 (2006.01) *A61K 31/16* (2006.01)
A61K 31/56 (2006.01)

(21) International Application Number:
PCT/US2005/044416

(22) International Filing Date:
7 December 2005 (07.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/634,449	8 December 2004 (08.12.2004)	US
60/660,924	10 March 2005 (10.03.2005)	US
60/660,904	11 March 2005 (11.03.2005)	US
60/672,405	18 April 2005 (18.04.2005)	US
60/698,512	11 July 2005 (11.07.2005)	US

(71) Applicant *(for all designated States except US)*: SYTERA, INC. [US/US]; 505 Coast Blvd., South, Suite 412, La Jolla, California 92037 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WIDDER, Kenneth [US/US]; P.O. Box 676250, Rancho Santa Fe, California 92067 (US). LICHTER, Jay [US/US]; 4950 Sandshore Ct., San Diego, California 92130 (US).

(74) Agents: HOSTETLER, Michael, J. et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, California 94304-1050 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, 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).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/063128 A2

(54) Title: METHODS, ASSAYS AND COMPOSITIONS FOR TREATING RETINOL-RELATED DISEASES

(57) Abstract: Described herein are methods and compositions for treating certain retinol-related diseases and conditions by modulation of transthyretin (TTR) and retinol binding protein (RBP) availability in the subject. For example, the methods and compositions provide for therapeutic agents for the treatment and/or prevention of age-related macular degeneration and/or dystrophies, metabolic disorders, idiopathic intracranial hypertension, hyperostosis, and protein misfolding and aggregation diseases. The compositions disclosed may be used as single agent therapy or in combination with other agents or therapies. In addition, described herein are methods and assays for selecting appropriate agents that can modulate the TTR and RBP availability in a subject.

METHODS, ASSAYS AND COMPOSITIONS FOR TREATING RETINOL-RELATED DISEASES

RELATED APPLICATIONS

[0001] This patent application claims the benefit of (a) U.S. Provisional Application Ser. No. 60/634,449, filed December 8, 2004, (b) U.S. Provisional Application Ser. No. 60/660,924, filed March 10, 2005, (c) U.S. Provisional Application serial number 60/660,904, filed on March 11, 2005, (d) U.S. Provisional Application serial number 60/672,405, filed on April 18, 2005, and (e) U.S. Provisional Application serial number 60/698,512, filed on July 11, 2005; the aforementioned patent applications are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The methods and compositions described herein are directed to the treatment of retinol-related diseases in a subject by modulating the activity or availability of retinol binding protein (RBP) and transthyretin (TTR) in the subject.

BACKGROUND OF THE INVENTION

[0003] Retinoids are essential for maintenance of normal growth, development, immunity, reproduction, vision and other physiological processes. Conversely, abnormal production or processing of retinoids correlates with the manifestation of disease processes.

[0004] For example, more than 100 million of the world's children are vitamin-A deficient, causing blindness and death among these children. Excess vitamin-A levels in target organs and tissues, such as the eye, may also cause blindness in a variety of retinal diseases, including macular degeneration. A large variety of conditions, generally referred to as vitreoretinal diseases, can affect the vitreous and retina that lie on the back part of the eye, including the retinopathies and macular degenerations and dystrophies. Macular degeneration is a group of eye diseases that is the leading cause of blindness for those aged 55 and older in the United States, affecting more than 10 million Americans. Some studies predict a six-fold increase in the number of new cases of macular degeneration over the next decade, taking on the characteristics of an epidemic. Age-related macular degeneration or dystrophy, a particularly debilitating disease, leads to gradual loss of vision and eventually severe damage to the central vision.

[0005] Abnormal levels of vitamin A, and/or its associated transport proteins (retinol binding protein (RBP) and transthyretin (TTR)) are also correlated with the manifestation of other diseases, including metabolic disorders. An example is seen in diabetes, where abnormal levels of retinol were seen in both type I and type II diabetic patients, but not normal patients. Other diseases include pseudotumor cerebri (PTC), idiopathic intracranial hypertension (IIH), and bone-related disorders, including cervical spondylosis, spinal hyperostosis, and diffuse idiopathic skeletal hyperostosis (DISH). In addition, vitamin A and/or its associated transport proteins, TTR in particular, may play a role in protein misfolding and aggregation diseases, including Alzheimer's disease and systemic amyloidosis.

[0006] Disorders associated with retinoid-related physiological manifestations continue to be a problem throughout the world. Therefore, there is a need to provide for methods and compositions to treat these diseases.

SUMMARY OF THE INVENTION

[0007] Described herein are methods and compositions for identifying and detecting agents which modulate retinol binding protein (RBP) or transthyretin (TTR) levels or activity in a mammal. Also described herein are assays for identifying compounds and therapeutic agents, as well as methods and compositions for treating a subject or patient with retinol-related diseases by administration of compounds or therapeutics agents, wherein said administration results in the modulation of RBP or TTR levels or activity in said patient or subject. Also described herein are methods and compositions for treating a patient with retinol-related diseases by modulating RBP or TTR levels or activity in the patient by administration of such compounds.

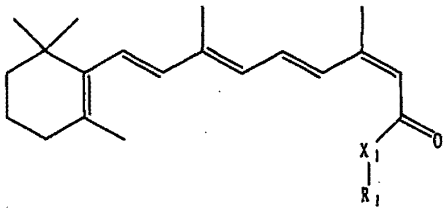
[0008] In one embodiment, the methods and compositions disclosed herein provide for the modulation of RBP or TTR levels or activity in a mammal comprising administering to the mammal at least once an effective amount of an agent which modulates RBP or TTR transcription in said mammal, wherein said modulation of RBP or TTR levels or activity reduces the formation of all-trans retinal in an eye of a mammal. In one embodiment, the agent is chosen from the group consisting of RXR/RAR agonists, RXR/RAR antagonists, estrogen agonists, estrogen antagonists, testosterone agonists, testosterone antagonists, progesterone agonists, progesterone antagonists, dexamethasone agonists, dexamethasone antagonists, antisense oligonucleotides, siRNA, fatty acid binding protein antagonists, C/EBP agonists, C/EBP antagonists, HNF-1 agonists, HNF-1 antagonists, HNF-3 agonists, HNF-3 antagonists, HNF-4 agonists, HNF-4 antagonists, HNF-6 agonists, HNF-6 antagonists, aptamers, Zn-finger binding proteins, ribozymes and monoclonal antibodies.

[0009] In yet another embodiment, the methods and compositions disclosed herein provide for modulating RBP or TTR levels or activity in a mammal comprising administering to the mammal at least once an effective amount of an RBP or TTR translation inhibitor, wherein said modulation of RBP or TTR levels or activity reduces the formation of all-trans retinal in an eye of a mammal. The agent may be chosen from the group consisting of: RXR/RAR agonists, RXR/RAR antagonists, estrogen agonists, estrogen antagonists, testosterone agonists, testosterone antagonists, progesterone agonists, progesterone antagonists, dexamethasone agonists, dexamethasone antagonists, antisense oligonucleotides, siRNA, fatty acid binding protein antagonists, C/EBP agonists, C/EBP antagonists, HNF-1 agonists, HNF-1 antagonists, HNF-3 agonists, HNF-3 antagonists, HNF-4 agonists, HNF-4 antagonists, HNF-6 agonists, HNF-6 antagonists, aptamers, ribozymes and monoclonal antibodies.

[0010] In one embodiment, the methods and compositions disclosed herein provide for modulating RBP or TTR levels or activity in a mammal comprising administering to the mammal at least once an effective amount of an agent which modulates RBP binding to TTR in said mammal, wherein said modulation of RBP or TTR levels or activity reduces the formation of all-trans retinal in an eye of a

mammal. The modulating agent can bind to RBP or TTR so as to inhibit the binding of RBP to TTR in the mammal. The modulating agent can also antagonize the binding of retinol to RBP so as to inhibit the binding of RBP or the RBP-agent complex to TTR. The modulating agent may be chosen from the group consisting of: a retinyl derivative, a polyhalogenated aromatic hydrocarbon, a thyroid hormone agonist, a thyroid hormone antagonist, diclofenac, a diclofenac analogue, a small molecule compound, an endocrine hormone analogue, a flavonoid, a non-steroidal anti-inflammatory drug, a bivalent inhibitor, a cardiac agent, a peptidomimetic, an aptamer, and an antibody.

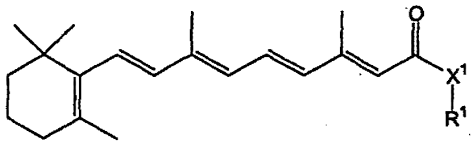
[0011] In one embodiment, the retinyl derivative of the methods and compositions disclosed herein is a compound having the structure:



(I),

wherein X_1 is selected from the group consisting of NR^2, O, S, CHR^2; R_1 is $(CHR^2)_x$-L^1-R^3, wherein x is 0, 1, 2, or 3; L^1 is a single bond or -C(O)-; R^2 is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -(C_1-C_4)alkylamine, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R^3 is H or a moiety, optionally substituted with 1-3 independently selected substituents, selected from the group consisting of (C_2-C_7)alkenyl, (C_2-C_7)alkynyl, aryl, (C_3-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, and a heterocycle; or an active metabolite, or a pharmaceutically acceptable prodrug or solvate thereof.

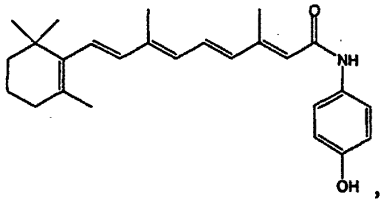
[0012] In one embodiment, the retinyl derivative of the methods and compositions disclosed herein is a compound having the structure:



(II);

wherein X^1 is selected from the group consisting of NR^2, O, S, CHR^2; R^1 is $(CHR^2)_x$-L^1-R^3, wherein x is 0, 1, 2, or 3; L^1 is a single bond or -C(O)-; R^2 is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -(C_1-C_4)alkylamine, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoroalkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R^3 is H or a moiety, optionally substituted with 1-3 independently selected substituents, selected from the group consisting of (C_2-C_7)alkenyl, (C_2-C_7)alkynyl, aryl, (C_3-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, and a heterocycle; or an active metabolite, or a pharmaceutically acceptable prodrug or solvate thereof.

[0013] In further embodiments (a) X^1 is NR^2, wherein R^2 is H or (C_1-C_4)alkyl; (b) x is 0; (c) x is 1 and L^1 is –C(O)-; (d) R^3 is an optionally substituted aryl; (e) R^3 is an optionally substituted heteroaryl; (f) X^1 is NH and R^3 is an optionally substituted aryl, including yet further embodiments in which (i) the aryl group has one substituent, (ii) the aryl group has one substituent selected from the group consisting of

halogen, OH, O(C_1-C_4)alkyl, NH(C_1-C_4)alkyl, O(C_1-C_4)fluoroalkyl, and N[(C_1-C_4)alkyl]$_2$, (iii) the aryl group has one substituent, which is OH, (v) the aryl is a phenyl, or (vi) the aryl is naphthyl; (g) the compound is  , or an active metabolite, or a pharmaceutically acceptable prodrug or solvate thereof; (h) the compound is 4-hydroxyphenylretinamide, or a metabolite, or a pharmaceutically acceptable prodrug or solvate thereof; (i) the compound is 4-methoxyphenylretinamide, or (j) 4-oxo fenretinide, or a metabolite, or a pharmaceutically acceptable prodrug or solvate thereof.

[0014] In further embodiments, the administration of a compound of Formula (II) is used to treat ophthalmic conditions by lowering the levels of serum retinol in the body of a patient. In further embodiments (a) the effective amount of the compound is systemically administered to the mammal; (b) the effective amount of the compound is administered orally to the mammal; (c) the effective amount of the compound is intravenously administered to the mammal; (d) the effective amount of the compound is ophthalmically administered to the mammal; (e) the effective amount of the compound is administered by iontophoresis; or (f) the effective amount of the compound is administered by injection to the mammal.

[0015] In further embodiments the mammal is a human, including embodiments wherein (a) the human is a carrier of the mutant *ABCA4* gene for Stargardt Disease or the human has a mutant *ELOV4* gene for Stargardt Disease, or has a genetic variation in complement factor H associated with age-related macular degeneration, or (b) the human has an ophthalmic condition or trait selected from the group consisting of Stargardt Disease, recessive retinitis pigmentosa, geographic atrophy (of which scotoma is one non-limiting example), photoreceptor degeneration, dry-form AMD, recessive cone-rod dystrophy, exudative (or wet-form) age-related macular degeneration, cone-rod dystrophy, and retinitis pigmentosa. In further embodiments the mammal is an animal model for retinal degeneration.

[0016] In further embodiments, are methods comprising multiple administrations of the effective amount of the agent which modulates RBP binding to TTR in said mammal, including further embodiments in which (i) the time between multiple administrations is at least one week; (ii) the time between multiple administrations is at least one day; and (iii) the compound is administered to the mammal on a daily basis; or (iv) the compound is administered to the mammal every 12 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[0017] In further embodiments are methods comprising administering at least one additional agent selected from the group consisting of an inducer of nitric oxide production, an anti-inflammatory agent, a physiologically acceptable antioxidant, a physiologically acceptable mineral, a negatively charged

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.