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WO 2004/026406 A1

(54) Title: USE OF CYTOKINE SYNTHESIS INHIBITORS FOR THE TREATMENT OF DRY EYE DISORDERS

(57) Abstract: Inhibitors of cytokine synthesis in nonimmune, resident ocular surface cells are useful for treating dry eye disorders and other disorders requiring the wetting of the eye.

USE OF CYTOKINE SYNTHESIS INHIBITORS FOR THE TREATMENT OF DRY EYE DISORDERS

The present invention is directed to the treatment of dry eye disorders. In particular, the present invention is directed to the use of certain cytokine synthesis inhibitors in the treatment of dry eye and other disorders requiring the wetting of the eye in mammals.

Background of the Invention

Dry eye, also known generically as *keratoconjunctivitis sicca,* is a common ophthalmological disorder affecting millions of Americans each year. The condition is particularly widespread among post-menopausal women due to hormonal changes following the cessation of fertility. Dry eye may afflict an individual with varying severity. In mild cases, a patient may experience burning, a feeling of dryness, and persistent irritation such as is often caused by small bodies lodging between the eye lid and the eye surface. In severe cases, vision may be substantially impaired. Other diseases, such as Sjogren's disease and *cicatricial pemphigoid* manifest dry eye complications.

Although it appears that dry eye may result from a number of unrelated pathogenic causes, all presentations of the complication share a common effect, that is the breakdown of the pre-ocular tear film, which results in dehydration of the exposed outer surface and many of the symptoms outlined above (Lemp, *Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes*, The CLAO Journal, volume 21, number 4, pages 221-231 (1995)).

Practitioners have taken several approaches to the treatment of dry eye. One common approach has been to supplement and stabilize the ocular tear film using so-called artificial tears instilled throughout the day. Other

approaches include the use of ocular inserts that provide a tear substitute or stimulation of endogenous tear production.

Examples of the tear substitution approach include the use of buffered, isotonic saline solutions, aqueous solutions containing water soluble polymers that render the solutions more viscous and thus less easily shed by the eye. Tear reconstitution is also attempted by providing one or more components of the tear film such as phospholipids and oils. Phospholipid compositions have been shown to be useful in treating dry eye; see, e.g., McCulley and Shine, *Tear film structure and dry eye*, Contactologia, volume 20(4), pages 145-49 (1998); and Shine and McCulley, *Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality*, Archives of Ophthalmology, volume 116(7), pages 849-52 (1998). Examples of phospholipid compositions for the treatment of dry eye are disclosed in U.S. Patent Nos. 4,131,651 (Shah et al.), 4,370,325 (Packman), 4,409,205 (Shively), 4,744,980 and 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.) and 5,578,586 (Glonek et al.). U.S. Patent No. 5,174,988 (Mautone et al.) discloses phospholipid drug delivery systems involving phospholipids, propellants and an active substance.

Another approach involves the provision of lubricating substances in lieu of artificial tears. For example, U.S. Patent No. 4,818,537 (Guo) discloses the use of a lubricating, liposome-based composition, and U.S. Patent No. 5,800,807 (Hu et al.) discloses compositions containing glycerin and propylene glycol for treating dry eye.

Although these approaches have met with some success, problems in the treatment of dry eye nevertheless remain. The use of tear substitutes, while temporarily effective, generally requires repeated application over the course of a patient's waking hours. It is not uncommon for a patient to have to apply artificial tear solution ten to twenty times over the course of the day. Such an undertaking is not only cumbersome and time consuming, but is also

potentially very expensive. Transient symptoms of dry eye associated with refractive surgery have been reported to last in some cases from six weeks to six months or more following surgery.

Aside from efforts directed primarily to the alleviation of symptoms associated with dry eye, methods and compositions directed to treatment of the dry eye condition have also been pursued. For example, U.S. Patent No. 5,041,434 (Lubkin) discloses the use of sex steroids, such as conjugated estrogens, to treat dry eye conditions in post-menopausal women; U.S. Patent No. 5,290,572 (MacKeen) discloses the use of finely divided calcium ion compositions to stimulate pre-ocular tear film production; and U.S. Patent No. 4,966,773 (Gressel et al.) discloses the use of microfine particles of one or more retinoids for ocular tissue normalization.

Some recent literature reports suggest that patients suffering from dry eye syndrome disproportionately exhibit the hallmarks of excessive inflammation in relevant ocular tissues, such as the lacrimal and meibomian glands. The use of various compounds to treat dry eye patients, such as steroids [*e.g.* U.S. Patent No. 5,958,912; Marsh, et al., *Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome*, Ophthalmology, 106(4): 811-816 (1999); Pflugfelder, *et. al.* U.S. Patent No. 6,153,607], cytokine release inhibitors (Yanni, J.M.; *et. al.* WO 0003705 A1), cyclosporine A [Tauber, J. *Adv. Exp. Med. Biol.* **1998**, *438* (Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2), 969], and 15-HETE (Yanni *et. al.*, US Patent No. 5,696,166), has been disclosed.

Summary of the Invention

The present invention is directed to methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. According to the methods of the present invention, certain cytokine synthesis

inhibitors are administered to a patient suffering from dry eye or other disorders requiring wetting of the eye. The cytokine synthesis inhibitors are preferably administered topically to the eye.

Brief Description of the Drawing

Fig. 1 shows the inhibition of hyperosmolarity-induced cytokine production from human corneal epithelial cells *in vitro* by SP-600125 and dexamethasone.

Detailed Description of the Invention

According to the present invention, inhibitors of cytokine synthesis by nonimmune resident ocular surface cells, including corneal and conjunctival epithelial and stromal cells, are administered to a patient suffering from dry eye. The compounds suitable for use in the present invention inhibit the synthesis of pro-inflammatory cytokines in nonimmune resident ocular surface cells by interfering with specific effectors of signaling cascades in these cells. Effectors of cytokine synthesis targeted for inhibition in the treatment of dry eye include mitogen-activated kinases (MAP kinase, p38 kinase), c-jun N-terminal kinase (JNK) and I-kappa kinase (IKK). Also, inhibitors of enzymes which convert precursors of the pro-inflammatory cytokines IL-1β (ICE, IL-1 converting enzyme) and TNFα (TACE, TNF-alpha converting enzyme) to the active species or inhibit the translation of cytokine mRNA provide dry eye therapy. Cytokines promote further synthesis of pro-inflammatory cytokines through activation of Janus family tyrosine kinase (JAK) and signal transducers and activators of transcription (STAT) and, therefore, inhibitors of JAKs and STATs provide treatment of dry eye. Inhibitors of activator protein-1 (AP-1) suppress cytokine synthesis in ocular surface cells and provide dry eye therapy. Additionally, ligands of retinoid X receptors (RXR) are known to suppress cytokine synthesis in epithelial cells and are suitable for use in the present invention.

The classes of cytokine synthesis inhibitors identified above are known. Inhibitors of MAP kinases (p38) include (5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole) ["SB-220025"]. Inhibitors of JNK include anthra[1,9-cd]pyrazol-6(2H)-one ["SP-600125"]. Inhibitors of ICE include pralnacasan (HMR3480/VX-740). TNF mRNA translation inhibitors include (D)Arginyl-(D)Norleucyl-(D)Norleucyl-(D)Arginyl-(D)Norleucyl-(D)Norleucyl-(D)Norleucyl-Glycine-(D)Tyrosine-amide,acetate salt ["RDP58"]. NFkB inhibitors include 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide ["SP-100030"], and triflusal. AP-1 inhibitors include SP-100030. RXR agonists include bexarotene.

Preferred cytokine synthesis inhibitors for use in the present invention are JNK inhibitors and AP-1 inhibitors.

According to the methods of the present invention, a composition comprising one or more of the specified cytokine synthesis inhibitors and a pharmaceutically acceptable carrier for topical ophthalmic administration or implantation into the conjunctival sac or anterior chamber of the eye is administered to a mammal in need thereof. The compositions are formulated in accordance with methods known in the art for the particular route of administration desired.

The compositions administered according to the present invention comprise a pharmaceutically effective amount of one or more of the specified cytokine synthesis inhibitors. As used herein, a "pharmaceutically effective amount" is one which is sufficient to reduce or eliminate signs or symptoms of dry eye or other disorders requiring the wetting of the eye. Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of cytokine synthesis inhibitor will be about 0.001 to 1.0% (w/w).

Preferably, the compositions administered according to the present invention will be formulated as solutions, suspensions and other dosage forms for topical administration. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid compositions. Suspensions may be preferred for cytokine synthesis inhibitors which are sparingly soluble in water.

The compositions administered according to the present invention may also include various other ingredients, including but not limited to surfactants, tonicity agents, buffers, preservatives, co-solvents and viscosity building agents.

Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, dextrose and/or mannitol may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150 – 450 mOsm, preferably 250 – 350 mOsm).

An appropriate buffer system (e.g., sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably, however, the buffer will be chosen to maintain a target pH within the range of pH 6-7.5.

Compositions formulated for the treatment of dry eye-type diseases and disorders may also comprise aqueous carriers designed to provide immediate, short-term relief of dry eye-type conditions. Such carriers can be formulated as a phospholipid carrier or an artificial tears carrier, or mixtures of both. As used herein, "phospholipid carrier" and "artificial tears carrier" refer to aqueous compositions which: (i) comprise one or more phospholipids (in the case of phospholipid carriers) or other compounds, which lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration; (ii) are safe; and (iii) provide the appropriate delivery vehicle for the topical administration of an effective amount of one or more of the specified cytokine inhibitors. Examples or artificial tears compositions useful as artificial tears carriers include, but are not limited to, commercial products, such as Tears Naturale®, Tears Naturale II®, Tears Naturale Free®, and Bion Tears® (Alcon Laboratories, Inc., Fort Worth, Texas). Examples of phospholipid carrier formulations include those disclosed in U.S. Patent Nos. 4,804,539 (Guo et al.), 4,883,658 (Holly), 4,914,088 (Glonek), 5,075,104 (Gressel et al.), 5,278,151 (Korb et al.), 5,294,607 (Glonek et al.), 5,371,108 (Korb et al.), 5,578,586 (Glonek et al.); the foregoing patents are incorporated herein by reference to the extent they disclose phospholipid compositions useful as phospholipid carriers of the present invention.

Other compounds designed to lubricate, "wet," approximate the consistency of endogenous tears, aid in natural tear build-up, or otherwise provide temporary relief of dry eye symptoms and conditions upon ocular administration the eye are known in the art. Such compounds may enhance the viscosity of the composition, and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, ethylene glycol; polymeric polyols, such as, polyethylene glycol, hydroxypropylmethyl cellulose ("HPMC"), carboxy methylcellulose sodium, hydroxy propylcellulose ("HPC"), dextrans, such as, dextran 70; water soluble proteins, such as gelatin; and vinyl polymers, such as, polyvinyl alcohol, polyvinylpyrrolidone, povidone and

carbomers, such as, carbomer 934P, carbomer 941, carbomer 940, carbomer 974P.

Other compounds may also be added to the ophthalmic compositions of the present invention to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers. In general, the phospholipid carrier or artificial tears carrier compositions will exhibit a viscosity of 1 to 400 centipoises ("cps").

Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of the present invention will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

The preferred compositions of the present invention are intended for administration to a human patient suffering from dry eye or symptoms of dry eye. Preferably, such compositions will be administered topically. In general, the doses used for the above described purposes will vary, but will be in an effective amount to eliminate or improve dry eye conditions. Generally, 1-2 drops of such compositions will be administered from once to many times per day.

A representative eye drop formulation is provided in Example 1 below.

Example 1

Ingredient	Amount (% w/w)
Cytokine synthesis inhibitor	0.001-1.0
Polyoxyl 40 Stearate	0.1
Boric Acid	0.25
Sodium Chloride	0.75
Disodium Edetate	0.01
Polyquaternium-1	0.001
NaOH/HCl	q.s., pH = 7.4
Purified Water	q.s. 100%

The above composition is prepared by the following method. The batch quantities of boric acid, sodium chloride, disodium edetate, and polyquaternium-1 are weighed and dissolved by stirring in 90% of the batch quantity of purified water. The pH is adjusted to 7.4 ± 0.1 with NaOH and/or HCl. The batch quantity of the cytokine synthesis inhibitor as a stock solution is measured and added. Purified water is added to q.s. to 100%. The mixture is stirred for five minutes to homogenize and then filtered through a sterilizing filter membrane into a sterile recipient.

Example 2: Inhibition of Hyperosmolarity-induced Cytokine Production from Human Corneal Epithelial Cells *in vitro.*

The ocular tear film in dry eye is abnormally hyperosmolar, which is irritating to ocular surface cells. Treatment of human conjunctival epithelial cells with a hypertonic media elicits the production of pro-inflammatory

cytokines. A selective JNK inhibitor, anthra[1,9-cd]pyrazol-6(2H)-one, was evaluated for inhibition of hyperosmolarity-induced cytokine secretion from the transformed human corneal epithelial cell line, CEPI-17. CEPI-17 cells were grown in complete isotonic Keratinocyte Growth Medium (iso KGM) and plated in 48-well plates in iso KGM without hydrocortisone (iso KGM-HC). When the cells reached confluence, they were pre-treated for 1 hour with the compound at the indicated concentration in iso KGM-HC. The cells were then stimulated by hypertonic KGM-HC for 6 hours (additional 80mM NaCl added in iso KGM-HC) in the presence of the compound. Aliquots of the supernatants were assayed for IL-6, IL-8 by ELISA. Cytokine release was normalized by the amount of double stranded DNA (dsDNA) extracted from the cells. Percent inhibition of cytokine production was calculated by comparison with cytokine levels in vehicle-treated cells. The results are shown in Figure 1. Hyperosmolarity significantly induced IL-6 and IL-8 production from CEPI-17 cells under the conditions described. Dexamethasone significantly inhibited secretion of each cytokine at 100nM. Anthra[1,9-cd]pyrazol-6(2H)-one (SP-600125) dose-dependently inhibited both IL-6 (IC_{50} = 12.6 μM) and IL-8 (IC_{50} = 3.7 μM) production.

This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. A method for the treatment of dry eye and other disorders requiring the wetting of the eye which comprises administering to a mammal a composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a cytokine synthesis inhibitor selected from the group consisting of mtiogen-activated kinase inhibitors; c-jun N-terminal kinase inhibitors; I-kappa kinase inhibitors; IL-1β synthesis inhibitors; TNF*α* synthesis inhibitors; Janus family tyrosine kinase inhibitors; signal transducers and activators of transcription inhibitors; and retinoid X receptor ligands.

2. The method of Claim 1 wherein the cytokine synthesis inhibitor is selected from the group consisting of MAP kinase inhibitors and p38 kinase inhibitors.

3. The method of Claim 1 wherein the cytokine synthesis inhibitor is selected from the group consisting of (5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole); anthra[1,9-cd]pyrazol-6(2H)-one; pralnacasan; (D)Arginyl-(D)Norleucyl-(D)Norleucyl-(D)Arginyl-(D)Norleucyl-(D)Norleucyl-(D)Norleucyl-Glycine-(D)Tyrosine-amide,acetate salt; 2-chloro-N-[3,5-di(trifluoromethyl)phenyl]-4-(trifluoromethyl)pyrimidine-5-carboxamide; triflusal; and bexarotene.

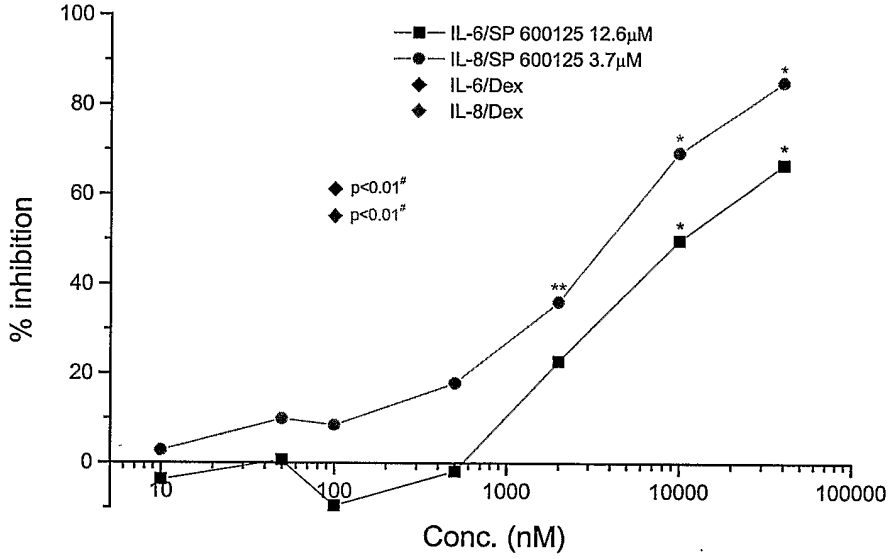
4. The method of Claim 1 wherein the cytokine synthesis inhibitor is selected from the group consisting of c-jun N-terminal kinase inhibitors and activator protein-1 inhibitors.

5. The method of Claim 1 wherein the pharmaceutically effective amount of the cytokine synthesis inhibitor is 0.001 – 1.0% (w/w).

6. The method of Claim 1 wherein the composition is topically administered to the eye.

7. The method of Claim 1 wherein the dry eye and other disorders requiring the wetting of the eye is symptoms of dry eye associated with refractive surgery.

Figure 1/1



Two-tail student t-test compared to vehicle control
* p<0.01, ** p<0.05 Two-tail Dunnett's t-test compared to vehicle control

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/26689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P27/02 A61K31/506 A61K31/192 A61K31/616 A61K31/551
A61K38/08 A61K31/416 A61K31/505

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 7 A61K

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 095704 A (ALCON INC ;YANNI JOHN M (US); GAMACHE DANIEL A (US)) 28 November 2002 (2002-11-28) claims 1-5	1,3-7
P,Y	claim 1	1,3,5-7
Y	EP 1 082 962 A (URIACH & CIA SA J) 14 March 2001 (2001-03-14) claim 1	1,3,5-7
P,X	WO 03 045225 A (SHUTO TSUYOSHI ;BASBAUM CAROL (US); KIM YOUNG S (US); LIM DAVID J) 5 June 2003 (2003-06-05) page 3, line 19-26 page 10, line 25-27; claim 4	1-3,5-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° 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 document 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
13 February 2004	04/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tardi, C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/26689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 26209 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); REVESZ LASZLO (CH)) 11 May 2000 (2000-05-11) page 28, line 7-18 page 31, line 6-21 page 32, line 23 -page 33, line 10; claim 5	1,2,5-7
Y	---	1-3,5-7
Y	JACKSON J R ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 284, no. 2, 1998, pages 687-692, XP002134931 ISSN: 0022-3565 abstract page 687, column 2, line 16-21 page 688, column 2, paragraph 4 page 689, column 1, paragraph 1	1-3,5-7
X	---	
	WO 00 03705 A (ALCON LAB INC) 27 January 2000 (2000-01-27) page 3, line 3-10 page 4, line 6-25 page 5, line 13-20; claims 1,13	1,5-7
X	---	
	WO 02 056888 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); GRAM HERMANN (DE);) 25 July 2002 (2002-07-25) page 3, line 23-28 page 4, line 10-22; claim 9	1,5-7
X	---	
	WO 02 13812 A (PERSHADSINGH HARRIHAR A) 21 February 2002 (2002-02-21) page 19, line 6-14 page 23, line 1-23; claims 1,24	1,3,5-7
Y	---	
	PFLUGFELDER S C ET AL: "THE DIAGNOSIS AND MANAGEMENT OF DRY EYE A TWENTY-FIVE-YEAR REVIEW" CORNEA, MASSON PUBL., NEW YORK, NY, US, vol. 19, no. 5, September 2000 (2000-09), pages 644-649, XP009003454 ISSN: 0277-3740 page 648, column 1, line 23-38	1-7

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	GOLDMAN M E ET AL: "SP100030 IS A NOVEL T-CELL-SPECIFIC TRANSCRIPTION FACTOR INHIBITOR THAT POSSESSES IMMUNOSUPPRESSIVE ACTIVITY IN VIVO" TRANSPLANTATION PROCEEDINGS, ORLANDO, FL, US, vol. 28, no. 6, December 1996 (1996-12), pages 3106-3109, XP001095817 ISSN: 0041-1345 page 3109, column 1, line 1-17 ---	1-7
Y	STERN M E ET AL: "THE PATHOLOGY OF DRY EYE: THE INTERACTION BETWEEN THE OCULAR SURFACE AND LACRIMAL GLANDS" CORNEA, MASSON PUBL., NEW YORK, NY, US, vol. 17, no. 6, November 1998 (1998-11), pages 584-589, XP009010472 ISSN: 0277-3740 abstract page 586, column 2, line 5-53 page 588, column 1, line 14-27 page 588, column 2, line 36-38 ---	1,3-7
Y	BENNETT BRYDON L ET AL: "SP600125, an anthrapyrazolone inhibitor of Jun N-terminal kinase" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 98, no. 24, 20 November 2001 (2001-11-20), pages 13681-13686, XP002270277 November 20, 2001 ISSN: 0027-8424 abstract page 13685, column 1, line 39-53 page 13686, column 2, line 23-30 -----	1,3-7

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3 (partially), 5-7(partially)

   a method of treatment of dry eye comprising the administration of MAP kinase (p38) inhibitors, e.g. SB-220025.

2. Claims: 1 (partially), 3-7 (partially)

   a method of treatment of dry eye comprising the administration of an inhibitor of JNK, e.g. SP-600125.

3. Claims: 1 (partially), 3 (partially), 5-7 (partially)

   a method of treatment of dry eye comprising the administration of ICE inhibitors, e.g. pralnacasan.

4. Claims: 1 (partially), 3 (partially), 5-7 (partially)

   a method of treatment of dry eye comprising the administration of TNFalpha synthesis inhibitors, e.g. RDP58.

5. Claims: 1 (partially), 3-7 (partially)

   a method of treatment of dry eye comprising the administration of NFkB or AP-1 inhibitors, e.g. SP-100030 and triflusal.

6. Claims: 1 (partially), 3 (partially), 5-7 (partially)

   a method of treatment of dry eye comprising the administration of RXR agonists, e.g. bexarotene.

Continuation of Box I.2

Present claims 1, 2 and 4-7 relate to compounds defined by reference to a desirable characteristic or property, namely
"a cytokine synthesis inhibitor"
"mitogen-activated kinase inhibitors"
"c-jun N-terminal kinase inhibitors"
"I-kappa kinase inhibitors"
"IL-1ß synthesis inhibitors"
"TNFalpha synthesis inhibitors"
"Janus family tyrosine kinase inhibitors"
"signal transducers and activators of transcription inhibitors"
"retinoid X receptor ligands"
"MAP kinase inhibitors"
"p38 kinase inhibitors"
"activator protein-1 inhibitors"

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in claim 3, taking into account the general concept on which the application is based.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/26689

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/26689

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