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(54) **Title**: METHOD OF TREATING AN OCULAR DISEASE AND COMPOSITIONS EFFECTIVE FOR TREATING AN OCULAR DISEASE

(57) **Abstract**: Methods and compositions are provided for treating an ocular disease in a subject in need thereof by increasing the bioavailability of a drug in the subjects eye. By one approach, the ocular disease is endophthalmitis. The methods and compositions provided herein include an efflux transporter inhibitor and a drug effective for treating the ocular disease. The efflux transporter inhibitor is effective to reduce the efflux of the drug through at least one of Pglycoprotein (Pgp), breast cancer resistant protein (BCRP), and multidrug resistant associated protein 19 (MRP19). In one aspect, cyclosporine A is the efflux transporter inhibitor.

METHOD OF TREATING AN OCULAR DISEASE AND COMPOSITIONS EFFECTIVE FOR TREATING AN OCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/636,143, filed April 20, 2012, which is incorporated herein by reference in its entirety.

FIELD

[0002] Methods and compositions are described for the treatment of ocular diseases in humans. More particularly, the methods and compositions include efflux transporter inhibitors and ocular drugs where the drugs are effective for the treatment of ocular diseases.

BACKGROUND

[0003] Many pharmacologic compositions for the treatment of ocular diseases are topically applied to the surface of the eye in the form of eye drops, gels, ointments or suspensions. The effectiveness of these pharmacologic compositions is limited, at least in part, by natural barriers present in the eye. It has been reported that bioavailability of ocular drugs within the eye is generally about 1 to 10 percent for topically administered drugs. For instance, the cornea is a known primary barrier for topical ocular drug delivery to the anterior segment of the eye. The primate cornea has five layers: epithelium, bowman's layer, stroma, descement's membrane, and endothelium. The epithelium includes tightly packed, stratified cells which forms a major barrier for drug permeation. It has been found that tight junctions and an array of drug efflux transporters in the epithelium are important factors for the poor delivery of ocular drugs. Efflux transporters play an important role in conferring drug resistance by pumping the drug compounds, such as antimicrobials, outside the cell by an energy-dependent mechanism.

[0004] Efflux transporters identified in the cornea include P-glycoprotein (Pgp), breast cancer resistant protein (BCRP), and multidrug resistant associated proteins 1–9 (MRPs 1–9). While not wishing to be bound by theory, it is presently believed that MRPs are considered to play a significant role in drug efflux compared to Pgp and BCRP in the cornea. The presence of these efflux transporters on the cornea has been found to confer drug resistance to a variety of

topically applied drugs. The presence of MRPs, Pgp and BCRP efflux pumps on cornea imply the likelihood of drug resistance to a wide range of ocular drugs. Corneal efflux pumps can also act in an additive manner to efflux a wider range of drug molecules, forming a very strong physical barrier for ocular drug delivery.

[0005] Pgp belongs to the ATP-binding cassette (ABC) family of transporters which use ATP as an energy source. This efflux transporter has two transmembrane sites embedded in the lipid bilayer of the cell membrane. Each transmembrane site includes six transmembrane domains. Pgp has two nucleotide binding domains which are also known as ATP binding domains.

[0006] MRPs appear to play a major role in drug efflux and the resulting decrease in drug efficacy. MRPs are also classified in the ABC family of transporters and require ATP for efflux function. The major structural difference between MRPs and Pgp is the presence in MRPs of an additional transmembrane site in the lipid bilayer, which includes five transmembrane domains. Additionally, another significant difference between the two transporters is the presence in MRP of an amino terminal on the external side of cell membrane.

[0007] BCRP was recently identified in human corneal epithelial cells. BCRP also primarily employs ATP for its efflux function. BCRP is referred to as a "half transporter" and has one transmembrane site and one ATP binding site. The transmembrane site has six transmembrane domains embedded in the lipid bilayer.

[0008] The relative rate of efflux through the corneal epithelium is governed by multiple factors, such as the drug substrate specificity with the efflux transporter and the extent of expression of a particular efflux transporter compared to other efflux transporters.

[0009] The treatment of ocular diseases is significantly limited by the difficulty in delivering effective doses of drugs to the target areas of the eye due to the presence of the efflux transporters. Further, the relatively small proportion of a topically applied pharmacologic composition that reaches the necessary site in the eye for activity often requires administration of high concentrations of the pharmacologic composition, which can lead to a variety of undesirable side effects.

SUMMARY

[0010] Described herein are methods and compositions for treating an ocular disease in a subject. It has been found that inhibition of the drug efflux transporters in the corneal epithelium significantly improves bioavailability of many ocular drugs. The methods and compositions provided herein include an efflux transporter inhibitor in combination with at least one ocular drug, where the combination of the efflux transporter inhibitor and one at least one ocular drug is effective for the treatment of an ocular disease. In this aspect, an efflux transporter inhibitor can be incorporated into a treatment regimen to be used in conjunction with an ocular drug. It has not previously been demonstrated that employing drug efflux inhibition is effective to treat ophthalmic disease in humans.

[0011] By one approach, a method is provided for treating an ocular disease in a subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising applying a therapeutically effective amount of a drug and an efflux transporter inhibitor, the amount of efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea. By one approach, the drug and efflux transporter inhibitor are applied topically to the subject's eye. In one aspect, the subject is a human.

[0012] In one aspect, the ocular disease is endophthalmitis, which can lead to blindness in chronic state, even when aggressively treated by conventional therapies. Accordingly, a method is provided for treating endopthalmitis in a subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising applying a therapeutically effective amount of a drug and an efflux transporter inhibitor, the amount of efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea. By one approach, the drug and efflux transporter inhibitor are applied topically to the subject's eye. In one particular aspect, the efflux transporter inhibitor is cyclosporine A and the drug comprises an antimicrobial. In one aspect, the subject is a human.

[0013] The efflux transporter inhibitor used in the methods and compositions described herein is effective to reduce the efflux of the drug through at least one efflux transporter in the cornea selected from the group consisting of P-glycoprotein (Pgp), breast cancer resistant protein (BCRP), and multidrug resistant associated proteins 1-9 (MRP1-9).

[0014] In some approaches, the amount of efflux transporter inhibitor included in the methods and compositions described herein is effective to reduce the efflux of the drug through the subject's cornea to improve the therapeutic efficacy of the drug when administered in a given quantity.

[0015] Generally, the time between application of the efflux transporter inhibitor and the drug, the relative amounts of the efflux transporter inhibitor and the drug, and the ratio of the efflux transporter inhibitor to the drug are effective to increase the therapeutic efficacy of the drug for treating the ocular disease as compared to administering the same amount of the drug without the efflux transporter inhibitor. In one aspect, the efflux transporter inhibitor is administered before administration of the drug, such as within minutes of administration of the efflux transporter inhibitor.

[0016] A composition for the treatment of an ocular disease in a subject is also described herein. By one approach, the composition comprises an efflux transporter inhibitor and at least one ocular drug, the drug included in a therapeutic amount for the treatment of the ocular disease. The relative amounts of the efflux transporter inhibitor and the drug, as well as the ratio of the efflux transporter inhibitor to the drug, in the composition are effective for increasing a therapeutic efficacy of the drug for treating the ocular disease as compared to administering the same amount of the drug without the efflux transporter inhibitor. In one aspect, the ocular disease is one that can be treated by an antimicrobial. In another aspect, the drug is an antibiotic. In another aspect, the drugs include ceftazidine, ciprofloxacin, vancomycin, or moxifloxacin. In another aspect, the efflux transporter inhibitor is cyclosporine A. In yet another aspect, the composition is effective for the treatment of endophthalmitis.

DETAILED DESCRIPTION

[0017] Described herein are methods and compositions for treating an ocular disease in a subject by increasing the ocular bioavailability of a drug by modulating the efflux of the drug through the subject's cornea. It has been discovered that there are significant benefits in drug efficacy, and also treatment of certain diseases, by incorporating drug efflux transporter modulators in ophthalmic compositions and/or treatment regimens. In some approaches, modulation of the efflux transporters is by inhibition. It has been found that inhibition of the drug efflux transporters in the corneal epithelium can significantly improve bioavailability of

many ocular drugs, thereby significantly increasing the efficacy of the ocular drug. Conventional ocular therapies do not involve use of efflux transporter inhibitors in conjunction with other medicaments.

[0018] Endophthalmitis is an inflammation and infection of tissues in the eye, often as a result of microbial infection after surgery or eye trauma. The inflammation generally affects the vitreous fluid in the center of the eye but can also affect neighboring areas of the eye responsible for vision. Symptoms of endopthalmitis include, for example, blurred vision, eye pain, and redness. In many instances, the loss of vision is irreversible. Endophthalmitis is typically treated with intraocular antibiotics and anti-inflammatory agents. In severe endophthalmitis, blindness can occur despite treatment.

[0019] By one approach, a method is provided for treating an ocular disease in a subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising applying a therapeutically effective amount of a drug and an efflux transporter inhibitor to the subject's eye, the efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea. By one approach, the drug and efflux transporter inhibitor are applied topically to the subject's eye. In one aspect, the subject is a human. In one aspect, the ocular disease is endophthalmitis.

[0020] By another approach, a method is provided for treating endopthalmitis in a subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising applying a therapeutically effective amount of a drug and an efflux transporter inhibitor to a subject's eye, the amount of efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea. By one approach, the drug and efflux transporter inhibitor are applied topically to the subject's eye. In one particular aspect, the efflux transporter inhibitor is cyclosporine A and the drug comprises an antimicrobial. In one aspect, the subject is a human.

[0021] By one approach, the time between application of the efflux transporter inhibitor and the drug, the relative amounts of the efflux transporter inhibitor and the drug, and the ratio of the efflux transporter inhibitor and the drug are effective to increase the therapeutic efficacy of the drug for treating the ocular disease as compared to administering the same amount of the drug without the efflux transporter inhibitor.

[0022] At least in some approaches, the drug and efflux transporter inhibitor are applied to the subject's eye at substantially the same time. By "substantially the same time" is meant within about 10 minutes, in another aspect within about 5 minutes, in another aspect within about 1 minute, and in another aspect within about 0.5 minutes.

[0023] As used herein, the term "treating" refers to an intervention performed to alter the pathology of, and thereby substantially alleviate or reduce in severity, an ocular disease or condition, including one or more symptoms of such disease or condition in a subject. As used herein, the term "subject" includes mammals and specifically includes humans. Veterinary applications are also contemplated. Accordingly, "treating" refers to both therapeutic treatment and prophylactic measures. The related term "treatment," as used herein, refers to the act of treating a symptom, disease or condition. Those in need of treatment include subjects already having an ocular disorder or ocular disease. By some approaches, the subject is in recognized need of treatment. For example, the subject may exhibit symptoms of ocular disease. In one aspect, the subject has been diagnosed by a medical professional as having an ocular disease or displaying symptoms of an ocular disease. In one aspect, the ocular disease is endopthalmitis. In another aspect, the ocular disease or condition is glaucoma, cataracts, or ocular herpes.

[0024] As used herein, the terms "therapeutically effective amount" or "effective amount" refer to the amount of drug and/or efflux transporter modulator required to confer a biological or meaningful patient benefit, such as the biological or medical response or improvement sought by a medical doctor or other medical professional. In one aspect, the terms "therapeutically effective amount" or "effective amount" are intended to mean the amount of drug and/or efflux transporter modulator that will bring about a biologically meaningful improvement in the subject's ocular disorder, symptom, or disease. Doses that exhibit large therapeutic indices are preferred. Effective amounts may vary, as recognized by those skilled in the art, depending, for example, on route of administration, dosage form, inclusion of additional active agents, as well as age, weight, sensitivity, and health of the subject.

[0025] As used herein, the term "efflux transporter inhibitor" means a chemical compound, protein, peptide, or other molecule that is effective to stop or reduce extrusion of a drug outside the cell via at least one efflux transporter in the subject's cornea. In some approaches, the efflux transporter inhibitor is effective to stop or reduce extrusion of a drug via at least one efflux transporter selected from the group consisting MRPs, BCRP, and Pgp of the

corneal epithelium. Examples of efflux transporter inhibitors include, for example, MK-571 ($C_{26}H_{26}ClN_2O_3S_2$. Na; a specific MRP inhibitor sold by Biomol International L.P. (PA, USA)), ketoconazole (a specific Pgp inhibitor), GF120918 (a specific Pgp inhibitor marketed as Elacridar by Santa Cruz Biotechnology), indomethacin, PGP-4008, bimatoprost (marketed as LUMIGAN® by Allergan), latanoprost (marketed as XALATAN® by Pfizer), sulfinpyrazone (a MRP5 modulator), and cylosporin-A (a Pgp inhibitor marketed as RESTASIS® by Allergan). Advantageously, cyclosporin-A may be used in the methods and compositions described herein as it is FDA approved for ocular use. Very strong substrates for the efflux transporters can act as inhibitors. Therefore, additional efflux transporter inhibitors can be designed and identified by one of ordinary skill in the art.

[0026] It has been found that efflux transporters (such as MPR and Pgp) sometimes act in conjunction to efflux certain drugs, and the combined activity of the efflux transporters forms a strong physical barrier against ocular drug delivery. In some approaches, use of a combination of efflux transporter inhibitors can result in an at least additive increase in uptake of drugs. While not wishing to be limited by theory, it is presently believed that MRP plays a more significant role compared to Pgp in ocular drug efflux of macrolides. Also not wishing to be limited by theory, it is presently believed that MRP4/MRP5 transporters play a significant role in the efflux of nucleoside and nucleotide analogues. It has also been demonstrated that efflux inhibitor GF120918 interacts with both BCRP and Pgp.

[0027] The efflux transporter inhibitor should be selected in conjunction with the drug selected for the particular treatment regimen. For example, it is known that erythromycin is a good substrate for MRP efflux but not a good substrate for Pgp efflux. Therefore, an efflux transporter inhibitor would be selected that inhibits MRP efflux. Selection of an efflux transporter inhibitor that inhibits Pgp efflux but not MRP efflux would not be expected to provide the desired clinical benefit. Also, for example, MK-571 is non-specific inhibitor for MRP1–9 but not for Pgp and BCRP. Therefore, MK-571 would be used in conjunction with a drug that is a substrate for MRP1–9 but not for Pgp and BCRP. As another example, MRP2 and MRP5 are involved in acyclovir efflux so an MRP inhibitor, such as MK-571, would be appropriate for treatment with acyclovir. Two widely used glaucoma drugs, bimatoprost and latanoprost, are both substrates for MRP5 and can suppress efflux of drugs administered therewith that are also substrates of MRP5.

[0028] In one aspect, the efflux transporter inhibitor is applied in an amount effective to reduce the efflux of the drug through the subject's cornea for a period of time sufficient for the administered drug to have clinical benefit to the patient.

[0029] As used herein, "drug" comprises at least one active ingredient, including, for example, compound, protein, peptide, or prodrug compound, that is effective to ameliorate or reduce one or more symptoms of an ocular disease. In one aspect, the efficacy of the drug is substantially increased when used in conjunction with an efflux transporter inhibitor. In one aspect, the drug is a substrate of at least one efflux transporter selected from the group consisting of MRPs, BCRP, and Pgp. In some approaches, the active ingredient includes at least one of an antimicrobial (including, for example, antibiotic, antifungal, and antiviral compounds). Exemplary antimicrobials include, for example, amoxicillin, ciprofloxacin, moxifloxacin, cephalexin, vancomycin, ceftazidime, amphotericin, doxycycline, tobramycin, amikacin, gentamicin, clindamycin, cefazolin, ceftazimide, ceftriaxone, cefotaxime, choramphenicol, erythromycin, oflaxacin, gatifloxacin, acyclovir (also called acycloguanosine and marketed as ZOVIRAX® by GlaxoSmithKline LLC), and combinations thereof.

[0030] When the ocular disorder being treated is endophthalmitis, ameliorating or reducing one or more symptoms of endophthalmitis includes, for example, reducing eye redness, eye pain, and improving blurred or lost vision.

[0031] In some approaches, the methods and/or compositions described herein may further include a second active ingredient in addition to the antimicrobial active agent and efflux transporter inhibitor. In one aspect, the second active ingredient may include, for example, a steroid or anti-inflammatory agent. Steroids useful in the methods and compositions described herein include, for example, hydrocortisone, flurometholone (FML), flurometholone acetate (FLAREX®), prednisolone sodium phosphate (marketed as Predsol), prednisolone actetate (PRED FORTE®), and dexamethasone (MAXIDEX™). The second active ingredient can be provided in the same or different drug as the antimicrobial active agent.

[0032] By some approaches, the drug can include both an antimicrobial and a second active ingredient. By other approaches, it is contemplated that the antimicrobial and second active agent are provided in separate compositions and are separately applied to the eye. In some approaches, at least two of the group consisting of antimicrobial, steroid, and anti-

inflammatory are used in combination with an efflux transporter inhibitor.

[0033] In one aspect, the drug may be applied directly to a target tissue, in one aspect the subject's cornea, or to a surrounding fluid or tissue. By some approaches, administration to the desired location may be by topical application.

[0034] The drug can be prepared in a variety of forms. For example, a liquid formulation can be prepared, such as, for example, in the form of a solution, emulsion, or suspension in a non-toxic, pharmaceutically-acceptable carrier. In another aspect, the drug may be a powder or lyophilisate that is reconstituted with a solvent prior to use. In yet another aspect, the formulation may be in the form of an emulsion or liquid concentrate that is suitable for dilution prior to administration. Exemplary pharmaceutically-acceptable carriers include saline, buffered saline, isotonic saline, Ringer's solution, dextrose, sterile water, deionized water, glycerol, ethanol, 5% dextrose in water, and combinations thereof.

[0035] The drug may comprise a variety of optional ingredients. For example, the topical formulation may include ingredients such as but not limited to preservatives, lubricant, stabilizer, colorant, diluent, isotonic agent, pH modifier, buffer, excipient, and the like and additional active ingredients, if desired. In one aspect, any additional ingredients included in the composition should not negatively impact the stability of the active ingredient(s) in the drug.

[0036] The treatment regimen for the ocular disease can vary depending on the particular needs of the subject. For example, the dose and frequency of administration of the drug and efflux transporter inhibitor may depend in part on the age of the subject and severity of ocular disease. By way of non-limiting illustration, the combination of drug and efflux transporter inhibitor may be applied at least once daily. By another approach, the combination of drug and efflux transporter inhibitor may be applied at least twice a day. Some subjects may benefit from regular application of the formulation, such as for at least about 3 days, in another aspect at least about 10 days. A shorter or longer treatment regimen may be used, if desired.

[0037] The combination therapy of drug and efflux transporter inhibitor can be administered to a subject for improved ocular drug bioavailability and therapeutic efficacy for the treatment of other ocular diseases, including, for example, cataracts, glaucoma, and ocular herpes.

[0038] Advantages and embodiments of the method and compositions described herein are further illustrated by the following example; however, the particular conditions, processing schemes, compositions, and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this method. All percentages are by weight unless otherwise indicated. All references listed herein are incorporated herein by reference in their entireties.

Example

Combination therapy treatment method

[0039] A uniocular 87 year old female subject was diagnosed with severe endophthalmitis in her only functioning eye. The subject presented with opacity behind the lens. The subject was non-responsive to the initial treatment regimen. The subject was treated with an aggressive treatment regimen of antibiotics (Intra Vitreal injection of Vancomycin and Ceftazidime) followed by Ceftazidime eye drops, Vancomycin eye drops and steroid Prednisolone eye drops every two hours. The subject showed no improvement over the next two days. The subject was at risk of total vision loss in the diseased eye.

[0040] Cyclosporin A (sold as RESTASIS® from Allergan, Inc.) was added to the treatment regimen and was administered prior to administering the antibiotic and steroid eye drops. A 16 mg dose of dexamethasone I.M. injection (8 mg in each arm) was given to the subject to decrease inflammation and the subject was asked to administer Gatifloxacin (500 mg table/day for seven days), which has been shown to cross the blood-retina barrier. The treatment regimen was administered with the hypothesis that it would result in inhibition of drug efflux barrier on the blood ocular barrier resulting in elevated posterior segment drug concentrations.

[0041] The subject's visual acuity improved dramatically by the next day. The next day the subject was given antibiotic Ceftriaxone (500 mg I.M.) injection and told to continue to use the cyclosporine A antibiotic/steroid eye drops. The Ceftriaxone was added to the regimen to increase the aggressiveness of the therapy with the goal of preventing or eliminating any traces of infection in the retina, which can result in irreversible blindness. Further, it was hypothesized that inhibition of drug efflux barrier on the blood ocular barrier will result in elevated vitreous concentration of Ceftriaxone antibiotic.

[0042] Within three to four days after addition of cyclosporine A of the regimen, the subject showed significant signs of improving vision with no visible signs of ocular inflammation and two weeks later showed a marked improvement in vision. Within the next few weeks, the patient regained 20/50 vision with no signs of endophthalmitis. The infection cleared and the subject's visual acuity was good upon reexamination nearly a year after the treatment. The restoration of the subject's vision is of high clinical significance because it is believed that less than 5 percent of endoopthalmitis patients report vision restoration to this extent.

[0043] While this disclosure has been particularly described with specific reference to particular processes and embodiments, it will be appreciated that various alterations, modifications, and adaptations may be based on the present disclosure, and are intended to be within the spirit and scope of the disclosure as defined by the following claims.

CLAIMS

What is claimed is:

1. A method for treating an ocular disease in a human subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising applying a therapeutically effective amount of a drug and an efflux transporter inhibitor, the amount of efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea.

2. The method according to claim 1, wherein the drug and efflux transporter inhibitor are topically applied to the subject's eye.

3. The method according to claim 1 or 2, wherein the efflux transporter inhibitor is effective to reduce the efflux of the drug through at least one efflux transporter selected from the group consisting of P-glycoprotein (Pgp), breast cancer resistant protein (BCRP), and multidrug resistant associated protein 1-9 (MRP1-9).

4. The method according to any one of claims 1 to 3, wherein the drug is an antimicrobial.

5. The method according to any one of claims 1 to 4, wherein the ocular disease is selected from the group consisting of endophthalmitis, glaucoma, and ocular herpes.

6. The method according to any one of claims 1 to 5, wherein the ocular disease is endophthalmitis.

7. The method according to any one of claims 1 to 6, wherein the efflux transporter inhibitor is cyclosporine A.

8. The method according to any one of claims 1 to 7, wherein the efflux transporter inhibitor and drug are administered at substantially the same time.

9. A method for treating endophthalmitis in a subject in need thereof by increasing the bioavailability of a drug in the subject's eye, the method comprising administering to the subject's eye an efflux transporter inhibitor and a therapeutically effective amount of a drug which is effective for the treatment of endophthalmitis, the amount of efflux transporter inhibitor applied in an amount effective to reduce the efflux of the drug through the subject's cornea.

10. The method according to claim 9, wherein the efflux transporter inhibitor is cyclosporine A.

11. The method according to claim 9 or 10, wherein the efflux transporter inhibitor and drug are administered at substantially the same time.

12. The method according to any one of claims 9 to 11, wherein the drug and efflux transporter inhibitor are topically applied to the subject's eye.

13. The method according to any one of claims 9 to 12, wherein the efflux transporter inhibitor is effective to reduce the efflux of the drug through at least one efflux transporter selected from the group consisting of P-glycoprotein (Pgp), breast cancer resistant protein (BCRP), and multidrug resistant associated protein 1-9 (MRP1-9).

14. The method according to any one of claims 9 to 13, wherein the drug is an antimicrobial.

15. A composition for the treatment of an ocular disease in a subject, the composition comprising:

an ocular drug; and

an efflux transporter inhibitor,

the amount of efflux transporter inhibitor in an amount effective to reduce the efflux of the drug through the subject's cornea, and the amount of drug effective to reduce or ameliorate at least one symptom of the ocular disease.

16. The composition according to claim 15, wherein the efflux transporter inhibitor is cyclosporine-A and the drug is an antibiotic.

17. The composition according to claim 15 or 16, wherein the drug is an antibiotic.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/032187

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/13 (2013.01)
USPC - 514/1.2
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 31/352, 31/7048, 38/00, 38/13, 45/06; C07K 14/705; C12Q 1/6876, 1/6883; G06F 19/20, 19/22 (2013.01)
USPC - 424/9.1; 435/320.1, 375, 6.11, 6.14; 514/1.2; 536/23.1; 702/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC - A61K 31/352, 31/7048, 38/00, 45/06; C07K 14/705; C12Q 1/6876, 1/6883; G06F 19/20, 19/22

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patbase, Google Patents, PubMed, Google Scholar, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0132457 A1 (BOSTIAN et al) 05 June 2008 (05.06.2008) entire document	1-3, 9-11, 15-17
Y	HARIHARAN et al. "Interaction of Ocular Hypotensive Agents (PGF2α Analogs—Bimatoprost, Latanoprost, and Travoprost) With MDR Efflux Pumps on the Rabbit Cornea," Journal of Ocular Pharmacology and Therapeutics, Vol. 25, No. 6, pp. 487-497. 2009. entire document	1-3, 9-11, 15-17
Y	US 2010/0222587 A1 (HUGHES et al) 02 September 2010 (02.09.2010) entire document	9-11
A	US 2007/0117750 A1 (ABDULRAZIK) 24 May 2007 (24.05.2007) entire document	1-3, 9-11, 15-17

☐ 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
17 May 2013	03 JUN 2013
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: Blaine R. Copenheaver 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/US2013/032187

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.: 4-8, 12-14
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:

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.:

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.