4. SUMMARY

[0014] The present disclosure provides methods for treating eye diseases, for example, eye diseases associated with lipid accumulation (*e.g.*, in subjects having ocular lipid deposits), using lipid binding protein-based complexes, for example CER-001. Other lipid binding protein-based complexes that can be used in the methods of the disclosure include Apomers, Cargomers, and HDL based complexes or HDL mimetic-based complexes such as CSL-111, CSL-112, ETC-216 or delipidated HDL. In some eye diseases, lipids may accumulate in the eye or near the eye (*e.g.*, lipids may accumulate in a subject's Meibomian gland or lacrimal gland). Exemplary eye diseases associated with lipid accumulation that can be treated by the methods of the disclosure include dry eye disease, such as dry eye disease associated with Meibomian gland dysfunction or lacrimal gland dysfunction, blepharitis, uveitis, diseases of the cornea such as lipid keratopathy, dry macular degeneration (dry AMD), Stargardt disease, Leber's idiopathic stellate neuroretinitis, and eye diseases associated with LCAT deficiency such as fish-eye disease. In some examples, the use of a lipid binding protein complex can reduce the severity of the eye disease. In some examples, the use of a lipid binding protein complex can slow the progression of the eye disease. Without being bound by theory, it is believed that a lipid binding protein complex can reduce ocular lipid deposits, for example by solubilizing the lipids accumulated in the ocular deposits, leading to their elimination. In one aspect, the present disclosure provides use of a lipid binding protein-based complex in the manufacture of a medicament for treating an eye disease in a subject, wherein the lipid binding protein-based complex (a) is CER-001 and/or (b) is a carrier for one or more ophthalmic drugs.

[0015] The present disclosure also provides methods of delivering ophthalmic drugs to the eye of a subject having an eye disease using a lipid binding protein-based complex (*e.g.*, CER-001) as a drug carrier, thereby treating the eye disease. For example, the subject can be a subject suffering from an anterior ocular condition or a posterior ocular condition, for example uveitis, macular edema, macular degeneration, retinal detachment, an ocular tumor, a fungal or viral infection, multifocal choroiditis, diabetic retinopathy, proliferative vitreoretinopathy (PVR), sympathetic ophthalmia, Vogt Koyanagi-Harada (VKH) syndrome, histoplasmosis, uveal diffusion, vascular occlusion, endophthalmitis, or glaucoma.

[0016] The present disclosure also provides compositions comprising a lipid binding protein-based complex (*e.g.*, CER-001) and one or more ophthalmic drugs complexed thereto.

[0016a] In another aspect, the present disclosure provides a process for making a composition comprising a lipid binding protein-based complex and one or more ophthalmic drugs, the process comprising thermal cycling a mixture comprising the lipid binding protein-based complex and the one or more ophthalmic drugs, optionally wherein (I) the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, ETC-216, CER-522, delipidated HDL, an Apomer, or a Cargomer and/or (II) one or more of the one or more ophthalmic drugs are (i) hydrophobic and/or (ii) poorly water soluble or water insoluble.

[0016b] In another aspect, the present disclosure provides a composition produced by a method comprising the process described herein, optionally wherein the composition is formulated as an eye drop.

[0016c] In another aspect, the present disclosure provides a composition comprising a lipid binding protein-based complex and one or more ophthalmic drugs complexed thereto, optionally wherein (I) the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, ETC-216, CER-522, delipidated HDL, an Apomer, or a Cargomer, preferably CER-001 and/or (II) one or more of the one or more ophthalmic drugs are (i) hydrophobic and/or (ii) poorly water soluble or water insoluble, optionally wherein the one or more ophthalmic drugs comprise a steroid, a kinase inhibitor, an angiotensin II receptor antagonist, an aldose reductase inhibitor, an immunosuppressant, a carbonic anhydrase inhibitor, an antimicrobial agent, an antiviral agent, an antihistamine, an anti-inflammatory, or a combination thereof, *e.g.*, dexamethasone palmitate (optionally at concentration in the composition of 1 mg/ml), azithromycin, dexamethasone, difluprednate, estradiol, fluocinolone, fluorometholone, hydrocortisone, loteprednol etabonate, prednisolone, triamcinolone, rimexolone, spironolactone, axitinib, BMS-794833 (N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide), carbozantinib, cediranib, dovitinib, lapatinib, lenvatinib, motesanib, nintedanib, orantinib, PD173074 (N-[2-[[4-(Diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyri- do[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea), pazopanib, regorafenib, sorafenib, tofacitinib, ZM323881 (5-((7-Benzyloxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol), candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, 2-methylsorbino, sirolimus, cyclosporine, tacrolimus, acetazolamide, brinzolamide, dorzolamide, ethoxzolamide, methazolamide, acyclovir, chloramphenicol, chlortetracycline, ciprofloxacin, fusidic acid, gancyclovir, norfloxacin, ofloxacin, tetracycline, zidovudine, levocabastine, bromfenac, diclofenac, indomethacin, nepafenac, or a combination thereof.

[0016d] In another aspect, the present disclosure provides use of the composition as described herein in the manufacture of a medicament for treating an eye disease in a subject

[0017] In the methods described herein, the lipid binding protein-based complex (*e.g.*, CER-001) can be administered systemically (*e.g.*, by infusion). Alternatively, the lipid binding protein-based complex (*e.g.*, CER-001) can be administered locally (*e.g.*, by intraocular or topical administration). Intraocular administration can be by, for example, intraocular injection, for example intra-vitreal injection, sub-conjuctival injection, parabulbar injection, peribulbar injection or retro-bulbar injection. For topical administration, the lipid binding protein-based complex (*e.g.*, CER-001) can be administered, for example, as an eye drop.

[0018] The present disclosure also provides dosing regimens for lipid binding protein-based complexes (*e.g.*, CER-001) for treating subjects with eye diseases associated with lipid accumulation. The dosing regimens described herein can also be applied to deliver ophthalmic drugs to the eye using a lipid binding protein-based complex (*e.g.*, CER-001) as a drug carrier.

[0019] The dosing regimens of the disclosure in some examples entail administering a lipid binding protein-based complex (*e.g.*, CER-001) to a subject according to an initial “induction” regimen, followed by administering the lipid binding protein-based complex (*e.g.*, CER-001) to the subject according to a “consolidation” regimen, followed by administering the lipid binding protein-based complex (*e.g.*, CER-001) to the subject according to a “maintenance” regimen. Alternatively, dosing regimens can entail administering a lipid binding protein-based complex (*e.g.*, CER-001) to the subject according to a “maintenance” regimen without a preceding “induction” regimen or “consolidation” regimen. As another alternative, dosing regimens can entail administering a lipid binding protein-based complex (*e.g.*, CER-001) to the subject according to an “induction” regimen followed by a “maintenance” regimen without an intervening “consolidation” regimen.

[0020] The induction regimen typically comprises administering multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject with a period of 1

day or greater between each dose. In some examples, the induction regimen comprises three or more doses of a lipid binding protein-based complex (*e.g.*, CER-001). In some examples, the induction regimen comprises three doses a week of a lipid binding protein-based complex (*e.g.*, CER-001). In some examples, the induction regimen comprises three doses a week of a lipid binding protein-based complex (*e.g.*, CER-001) for a period of more than one week *e.g.*, a period of two weeks or greater. In some examples the induction regimen comprises three doses a week of a lipid binding protein-based complexes (*e.g.*, CER-001) for a period of three weeks.

[0021] The consolidation regimen typically comprises administering multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject on a less frequent basis than during the induction regimen. The consolidation regimen typically comprises administering multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject with a period of 1 day or greater between each dose *e.g.*, 2 days or greater between each dose. In some examples, the consolidation regimen comprises two or more doses of a lipid binding protein-based complex (*e.g.*, CER-001). In some examples, the consolidation regimen comprises two doses a week of a lipid binding protein-based complex (*e.g.*, CER-001). In some examples, the consolidation regimen comprises two doses a week of a lipid binding protein-based complex (*e.g.*, CER-001) for a period of more than one week *e.g.*, a period of two weeks or greater. In some examples the consolidation regimen comprises two doses a week of a lipid binding protein-based complex (*e.g.*, CER-001) for a period of three weeks.

[0022] The maintenance regimen typically comprises administering one or more doses of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject on a less frequent basis than during the consolidation regimen, for example a period of 5 days or greater, *e.g.*, a period of one week, between doses. In certain examples, the multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) are administered once every week during the maintenance regimen.

[0023] In certain examples, the disclosure provides methods of treating a subject with lipid binding protein-based complexes (*e.g.*, CER-001) using an induction regimen comprising administering three doses of the lipid binding protein-based complexes (*e.g.*, CER-001) to the subject within one week for three weeks with at least 1 day between

each dose followed by a consolidation regimen comprising administering two doses of the lipid binding protein-based complex (*e.g.*, CER-001) to the subject within one week for three weeks with at least 2 days between each dose followed by a maintenance regimen comprising administering one dose of the lipid binding protein-based complex (*e.g.*, CER-001) to the subject every week.

[0024] In certain examples, the disclosure provides methods of treating a subject with a lipid binding protein-based complex (*e.g.*, CER-001) in accordance with a dosage regimen described herein. In some examples, the lipid binding protein-based complex (*e.g.*, CER-001) is diluted with saline before intravenous administration such as intravenous infusion using an infusion pump. In certain examples the dose of the lipid binding protein-based complex (*e.g.*, CER-001) for infusion is based on subject weight, for example 10 mg / kg on a protein weight basis.

[0025] In certain examples, the disclosure provides methods of treating a subject having an eye disease (*e.g.*, associated with lipid accumulation) with a lipid binding protein-based complex (*e.g.*, CER-001) according to a dosage regimen comprising:

- 3 doses per week for 3 weeks (induction regimen) followed by
- 2 doses per week for 3 weeks (consolidation regimen), followed by
- 1 dose per week until the end of treatment (maintenance regimen).

[0026] In certain examples, an antihistamine (*e.g.*, dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of the lipid binding protein-based complex (*e.g.*, CER-001), *e.g.*, when the lipid binding protein-based complex is administered by IV infusion. The antihistamine can reduce the likelihood of allergic reactions.

[0027] The subject treated according to the dosing regimens of the disclosure can be any subject suffering from an eye disease associated with lipid accumulation, for example a subject having LCAT deficiency. The LCAT deficiency may be full LCAT deficiency or partial LCAT deficiency. In some examples, the subject treated according to the dosing regimens of the disclosure has fish-eye disease. Alternatively, subjects treated according to the dosing regimens of the disclosure can also be any

WHAT IS CLAIMED IS:

1. Use of a lipid binding protein-based complex in the manufacture of a medicament for treating an eye disease in a subject, wherein the lipid binding protein-based complex (a) is CER-001 and/or (b) is a carrier for one or more ophthalmic drugs.

2. The use according to claim 1, wherein the eye disease is a disease associated with lipid accumulation, such as fish-eye disease, lipid keratopathy (optionally wherein the lipid keratopathy is secondary lipid keratopathy), or corneal dystrophy (*e.g.*, an inherited corneal dystrophy, an anterior or superficial corneal dystrophy, a stromal corneal dystrophy, or a posterior corneal dystrophy).

3. The use according to claim 1 or claim 2, wherein the subject has corneal opacity.

4. The use according to claim 1 or claim 2, wherein the eye disease is dry eye disease (optionally wherein the dry eye disease is (a) associated with Meibomian gland dysfunction (MGD), optionally wherein the MGD is obstructive MGD or (b) associated with lacrimal gland dysfunction), blepharitis, an inflammatory eye disease, uveitis (optionally wherein the uveitis is anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis), macular edema, macular degeneration, retinal detachment, an ocular tumor, a fungal infection, a viral infection, a bacterial infection (*e.g.*, bacterial conjunctivitis or trachoma), multifocal choroiditis, diabetic retinopathy, proliferative vitreoretinopathy (PVR), sympathetic ophthalmia, Vogt Koyanagi-Harada (VKH) syndrome, histoplasmosis, uveal diffusion, vascular occlusion, endophthalmitis, glaucoma, dry macular degeneration, wet macular degeneration, Stargardt disease, or diabetic retinopathy (optionally wherein the subject has diabetic macular edema).

5. The use according to any one of claims 1 to 4, wherein the subject has impaired vision due to the eye disease.

6. The use according to any one of claims 1 to 5, wherein the subject has ocular lipid deposits, optionally wherein the ocular lipid deposits comprise corneal lipid deposits, retinal lipid deposits, palpebral lipid deposits or a combination thereof.

7. The use according to any one of claims 1 to 6, wherein the lipid binding protein-based complex is CER-001.

8. The use according to any one of claims 1 to 7, wherein the lipid binding protein-based complex is a carrier for one or more ophthalmic drugs, optionally wherein (I) the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, ETC-216, CER-522,

delipidated HDL, an Apomer, or a Cargomer and/or (II) the one or more ophthalmic drugs are (i) hydrophobic and/or (ii) poorly water soluble or water insoluble, optionally wherein the one or more ophthalmic drugs comprise a steroid, a kinase inhibitor, an angiotensin II receptor antagonist, an aldose reductase inhibitor, an immunosuppressant, a carbonic anhydrase inhibitor, an antimicrobial agent, an antiviral agent, an antihistamine, an anti-inflammatory, a prostaglandin analog, or a combination thereof, *e.g.*, dexamethasone palmitate, azithromycin, dexamethasone, difluprednate, estradiol, fluocinolone, fluorometholone, hydrocortisone, loteprednol etabonate, prednisolone, triamcinolone, rimexolone, spironolactone, axitinib, BMS-794833 (N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide), carbozantinib, cediranib, dovitinib, lapatinib, lenvatinib, motesanib, nintedanib, orantinib, PD173074 (N-[2-[[4-(Diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyri- do[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea), pazopanib, regorafenib, sorafenib, tofacitinib, ZM323881 (5-((7-Benzyloxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol), candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, 2-methylsorbino, sirolimus, cyclosporine, tacrolimus, acetazolamide, brinzolamide, dorzolamide, ethoxzolamide, methazolamide, acyclovir, chloramphenicol, chlortetracycline, ciprofloxacin, fusidic acid, gancyclovir, norfloxacin, ofloxacin, tetracycline, zidovudine, levocabastine, bromfenac, diclofenac, indomethacin, nepafenac, latanoprost, travaprost, bimatoprost, or a combination thereof.

9. The use according to according to claim 8, wherein the lipid binding protein-based complex is CER-001.

10. The use according to any one of claims 1 to 9, wherein the medicament is formulated for peripheral administration, optionally by infusion.

11. The use according to any one of claims 1 to 9, wherein the medicament is formulated for local administration.

12. The use according to claim 11, wherein the medicament is formulated for intraocular administration, such as by intraocular injection, optionally wherein the intraocular injection is intra-vitreal injection, sub-conjunctival injection, parabulbar injection, peribulbar injection, or retro-bulbar injection; or topical administration, optionally wherein the lipid binding protein-based complex is formulated as an eye drop.

13. A process for making a composition comprising a lipid binding protein-based complex and one or more ophthalmic drugs, the process comprising thermal cycling a mixture comprising the lipid binding protein-based complex and the one or more ophthalmic drugs,

optionally wherein (I) the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, ETC-216, CER-522, delipidated HDL, an Apomer, or a Cargomer and/or (II) one or more of the one or more ophthalmic drugs are (i) hydrophobic and/or (ii) poorly water soluble or water insoluble.

14. The process of claim 13, wherein the thermal cycling comprises

(a) heating the mixture from a temperature in a first temperature range, such as 30°C to 45°C, *e.g.*, 37°C, to a temperature in a second temperature range, such as 50°C to 65°C, *e.g.*, 55°C,

(b) cooling the mixture of (a) from a temperature in the second temperature range to a temperature in the first temperature range; and

(c) optionally repeating steps (a) and (b) at least once, such as one, two, three, four, or five times.

15. The process of claim 14, which comprises thermal cycling the mixture between 37°C and 55°C.

16. A composition produced by a method comprising the process of any one of claims 13 to 15, optionally wherein the composition is formulated as an eye drop.

17. A composition comprising a lipid binding protein-based complex and one or more ophthalmic drugs complexed thereto, optionally wherein (I) the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, ETC-216, CER-522, delipidated HDL, an Apomer, or a Cargomer, preferably CER-001 and/or (II) one or more of the one or more ophthalmic drugs are (i) hydrophobic and/or (ii) poorly water soluble or water insoluble, optionally wherein the one or more ophthalmic drugs comprise a steroid, a kinase inhibitor, an angiotensin II receptor antagonist, an aldose reductase inhibitor, an immunosuppressant, a carbonic anhydrase inhibitor, an antimicrobial agent, an antiviral agent, an antihistamine, an anti-inflammatory, or a combination thereof, *e.g.*, dexamethasone palmitate (optionally at concentration in the composition of 1 mg/ml), azithromycin, dexamethasone, difluprednate, estradiol, fluocinolone, fluorometholone, hydrocortisone, loteprednol etabonate, prednisolone, triamcinolone, rimexolone, spironolactone, axitinib, BMS-794833 (N-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide), carbozantinib, cediranib, dovitinib, lapatinib, lenvatinib, motesanib, nintedanib, orantinib, PD173074 (N-[2-[[4-(Diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyri- do[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)urea), pazopanib, regorafenib, sorafenib, tofacitinib, ZM323881 (5-((7-Benzyloxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol), candesartan, irbesartan, losartan,

olmesartan, telmisartan, valsartan, 2-methylsorbino, sirolimus, cyclosporine, tacrolimus, acetazolamide, brinzolamide, dorzolamide, ethoxzolamide, methazolamide, acyclovir, chloramphenicol, chlortetracycline, ciprofloxacin, fusidic acid, gancyclovir, norfloxacin, ofloxacin, tetracycline, zidovudine, levocabastine, bromfenac, diclofenac, indomethacin, nepafenac, or a combination thereof.

18. The composition of claim 16 or claim 17, wherein the lipid binding protein-based complex is CER-001.

19. The composition of claim 16 or claim 17, which is a pharmaceutical composition further comprising one or more buffers, preservatives, excipients, diluents, or a combination thereof, optionally wherein the pharmaceutical composition is formulated as an eye drop.

20. Use of the composition of any one of claims 16 to 19 in the manufacture of a medicament for treating an eye disease in a subject.