Abstract:

Title: LOCAL DELIVERY OF IL-17 INHIBITORS FOR TREATING OCULAR DISEASE

Fig. 1

![Graph showing clinical and histologic scores]

1. Vehicle
2. Anti-IL-17
3. Cyclosporine

(57) Abstract: Disclosed is a method of treating ocular disease, e.g., uveitis by local administration of an IL-17 inhibitor alone or in combination with a systemically administered drug that is not a direct IL-17 inhibitor.
LOCAL DELIVERY OF IL-17 INHIBITORS FOR TREATING OCULAR DISEASE

RELATED APPLICATIONS

The present application claims priority to U.S. Application Serial No. 61/749,574, filed January 7, 2013. The entire content of the foregoing application is hereby incorporated herein by reference.

FIELD OF THE INVENTION

The field of the invention relates to compositions and methods for treating IL-17 related disease. More particularly, the field relates to local delivery of an IL-17 inhibitor to treat eye disease.

BACKGROUND

Uveitis refers to swelling and irritation of the uvea of the eye. Uveitis can be associated with a variety of disorders including autoimmune disorders or can be idiopathic. Effective methods of treating uveitis generally include systemic or local administration of corticosteroids. Both treatments can have undesirable effects. Thus, it is desirable to identify improved methods and compositions for treating uveitis.

SUMMARY

The invention relates to the discovery that local delivery of an IL-17 inhibitor is useful for treating eye diseases in which IL-17 plays a role, e.g., uveitis. Such IL-17 inhibitors can be administered as a sole treatment or in a regime that includes systemic treatment with, e.g., a corticosteroid, methotrexate, cyclosporine or analogous molecule, or an inhibitor of a tumor necrosis factor (TNF), e.g., infliximab. In some embodiments, the IL-17 inhibitor is a dominant negative variant of an IL-17.

Accordingly, the invention relates to a method of treating an ocular disease in a subject. The method includes administering a therapeutically effective amount of an IL-17 inhibitor to an affected eye of a subject. In some embodiments, the ocular disease is uveitis or AMD. In some embodiments, the IL-17 inhibitor is an antibody or a small molecule.
In some aspects, the invention relates to an IL-17 inhibitor formulated for local delivery for use in treating an ocular disease. In some embodiments, the ocular disease is uveitis or AMD. In some embodiments, the IL-17 inhibitor is an antibody or a small molecule.

The invention also relates to the use of an IL-17 inhibitor for the manufacture of a medicament for local treatment of an ocular disease. In some embodiments, the ocular disease is uveitis or AMD. In some embodiments, the IL-17 inhibitor is an antibody or small molecule. In some cases, the IL-17 inhibitor binds to an IL-17. In some cases, the IL-17 inhibitor binds to an IL-17 receptor.

In some embodiments, the invention relates to the use of an IL-17 inhibitor for the manufacture of a medicament for treating ocular disease, wherein the IL-17 inhibitor is prepared to be administered locally to the eye. In some embodiments, the ocular disease is uveitis or AMD. In some embodiments, the IL-17 inhibitor is an antibody or small molecule. In some cases, the IL-17 inhibitor binds to an IL-17. In some cases, the IL-17 inhibitor binds to an IL-17 receptor.

In some cases of the above embodiments, the subject is further treated systemically with a drug that is not a direct IL-17 inhibitor, e.g., cyclosporine A.

In some cases of the above embodiments, the IL-17 inhibitor is an antibody that can specifically bind an IL-17.

In some cases of the above embodiments, the IL-17 inhibitor is a dominant negative variant of IL-17.

In some cases of the above embodiments, the IL-17 inhibitor is administered intravitreally.

In some cases, the IL-17 inhibitor is administered topically to the eye.

The invention also relates to a polypeptide sequence comprising SEQ ID NO: 1 or SEQ ID NO:2.

The entire disclosure of each patent document and scientific article referred to herein, and those patent documents and scientific articles cited thereby, is expressly incorporated by reference herein for all purposes.
Additional features and advantages of the invention are more particularly described below.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph depicting the results of experiments in which a monoclonal antibody that binds to IL-17 (anti-IL17A mAb)(intravitreal), vehicle, or cyclosporine (oral) was administered to a rat EAU model. *p < 0.05, **p < 0.005 compared to vehicle.

DETAILED DESCRIPTION

Applicants have discovered that local delivery of an IL-17 inhibitor is useful for treating ocular disease involving IL-17, e.g., uveitis. In general, delivery is intravitreal, for example, by injection. The efficacy of a locally delivered IL-17 inhibitor is surprising because although systemic administration of an IL-6 inhibitor, an IL-1 inhibitor, or an IL-17 inhibitor have been reported as useful treatments for uveitis patients, applicants found that when locally delivered, neither an IL-6 inhibitor nor an IL-1 inhibitor improved symptoms of uveitis, demonstrating that a useful treatment using a systemically delivered compound, in particular a cytokine inhibitor, is not predictive of whether the compound will be effective when locally delivered.

In general, uveitis is treated systemically or locally with corticosteroids, which can have adverse effects on a patient. For example, local administration of a corticosteroid can increase intraocular pressure and cause glaucoma. An advantage of applicant's discovery is that local treatment of uveitis (i.e., delivery directly to the eye) with an IL-17 inhibitor limits undesirable side effects associated with systemic delivery of a drug, such as systemic immune suppression that can result in an increased risk of infection, for example, a corticosteroid, IL-6 inhibitor, IL-1 inhibitor, or an IL-17 inhibitor. Further, local administration of an IL-17 inhibitor can limit side effects that are associated with local treatment of uveitis using, e.g., a corticosteroid.

In some embodiments, the IL-17 inhibitor is locally delivered to the eye of a subject in need of treatment and the subject is also treated systemically with a drug that is not a direct inhibitor of IL-17, for example, a corticosteroid. As used herein, the term "subject" and "patient" are used interchangeably unless indicated otherwise by the context. The combination can provide a more effective treatment of the uveitis than corticosteroid alone. In certain embodiments, the
amount or duration of corticosteroid treatment is reduced when it is administered in a treatment regime in conjunction with an IL-17 inhibitor.

**IL-17 inhibitors**

An IL-17 inhibitor useful in the invention can be a pharmaceutical compound or a biologic. In general, such an inhibitor can specifically bind to an IL-17, e.g., can specifically bind to a human IL-17 such as an IL-17A or can specifically bind to an IL-17 receptor (IL-17R). In some embodiments, the IL-17 inhibitor binds to an IL-17 or an IL-17 receptor with a $K_D$ of less than 100 nM, 50 nM, 20 nM, 10 nM, 5 nM, or 1 nM, or less than 500 pM, 200 pM, 100 pM, or 50 pM. For example, the association constant can be greater than $1 \times 10^4$, $5 \times 10^4$, $1 \times 10^5$, or $1 \times 10^6 \text{M}^{-1} \text{s}^{-1}$, and/or the dissociation constant can be less than $1 \times 10^{-3}$, $5 \times 10^{-4}$, $1 \times 10^{-5}$, or $1 \times 10^{-6} \text{s}^{-1}$.

In some embodiments, the IL-17 inhibitor inhibits (e.g., decreases or prevents) at least one function of an IL-17 protein, such as a binding activity (e.g., receptor binding, dimerization), a signaling activity (e.g., inducing an immune signaling molecule or mediating a proinflammatory response, e.g., inducing the production of a cytokine (e.g., IL-6, G-CSF, GM-CSF, IL-1β, TGF-β, or TNF-a), a chemokine (e.g., IL-8, GRO-a, or MCP-1), and/or a prostaglandin (e.g., PGE2)), and/or a cellular response function (e.g., an allergic response, attraction of certain type of cells (e.g., neutrophils)). In some embodiments, the IL-17 inhibits an IL-17 activity, e.g., with a $K_i$ of less than $10^{-3}$, $10^{-4}$, $10^{-5}$, $10^{-6}$, $10^{-7}$, or $10^{-10}$ M. In some embodiments, the IL-17 inhibitor has an IC50 of less than 100 nM, 10 nM, or 1 nM.

Exemplary IL-17 inhibitors include, but are not limited to, antagonists which bind an IL-17 or an IL-17 receptor (e.g., an antibody, a polypeptide, a dominant negative variant of an IL-17, a mutant of a natural IL-17 receptor, a small molecular weight organic molecule, and a competitive inhibitor of receptor binding), and substances which inhibit one or more IL-17 functions without binding thereto (e.g., an anti-idiotypic antibody).

The specific binding of an IL-17 inhibitor to an IL-17 or an IL-17 receptor and/or the inhibition of one or more functions of an IL-17 protein can be determined by methods known in the art, e.g., using a cell-based assay, e.g., as described in US patent publication no. 20130064788 (see, e.g., Examples 7-9, which describe binding and activity assays performed in BHK, PBMC and NIH3T3 cells).
In some embodiments, the IL-17 inhibitor is a dominant negative variant of an IL-17 (e.g., PCT/US20 10/052 194), a polypeptide (e.g., as described in US patent publication no. 20130005659), or an antibody (e.g., as described in US patent application publication no 20120107325 or 20120129219, antibody fragment, or antibody variant, for example, a domain antibody, a bispecific antibody that has at least one site that can specifically bind to an IL-17 or IL-17R, a diabody, or other structure comprising CDRs derived from an antibody in non-antibody scaffolding. Additional, non-limiting examples of IL-17 inhibitors include ixekizumab, secukinumab, RG4936, and SCH-9001 17. In some embodiments, the inhibitor can bind to an IL-17 receptor, e.g., brodalumab.

Examples of IL-17 dominant negative molecules useful in the methods described herein and in other methods for which an IL-17 inhibitor is useful are shown in SEQ ID NO:1 (pi: 8.28, MW: 32205.8, Ext: 34670; triple mutation with disulfides) and SEQ ID NO:2 (pi: 8.44, MW: 32141, Ext: 34420; triple mutation without disulfides). Methods of demonstrating the IL-17 receptor binding and activity of such molecules are known in the art, e.g., see PCT/US20 10/052 194.

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GITIPRNPGCPNPSEDFKPRTVMVNLNIHNRNTNPKRSSDYYYYESTSPWNLHRNEDPE
RYPSVIWAEKCRHLGCINADGNVDYHMNSVPIQQEILVLRREPPHCPSFRLKILVSVG
CTCVTPIVHHVAGGGGGSGGGSGGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSG
GITIPRNPGCPNPSEDFKPRT
VMVNLNIHNRNTNPKRSSDYYYYNRSTPWNLHRNEDPERYPSVrWAEKCRHLGCINA
DGVSVDYHMRSVPIQQEILVLRREPPHCPSFRLKILVSVGGCTCVPASHHHHHH (SEQ
ID NO:1)
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GITIPRNPGCPNPSEDFKPRTVMVNLNIHNRNTNPKRSSDYYYYESTSPWNLHRNEDPE
RYPSVIWAEKCRHLGCINADGNVDYHMNSVPIQQEILVLRREPPHCPSFRLKILVSVG
CTCVTPIVHHVAGGGGGSGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG
GITIPRNPGCPNPSEDFKPRT
VMVNLNIHNRNTNPKRSSDYYYYNRSTPWNLHRNEDPERYPSVrWAEKCRHLGCINA
DGVSVDYHMRSVPIQQEILVLRREPPHCPSFRLKILVSVGGCTCVPASHHHHHH (SEQ
ID NO:2)
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**IL-17-related diseases of the eye**

**Uveitis**

Uveitis refers to swelling and irritation of the uvea of the eye. Uveitis can be associated with a variety of disorders including autoimmune disorders or can be idiopathic. Anterior uveitis, involves inflammation in the front of the uvea. Posterior uveitis affects the back the uvea, and involves primarily the choroid. Posterior uveitis affecting primarily the choroid can be referred to as choroiditis. If the retina is also involved, the disease can be referred to as chorioretinitis. Pars planitis is a form of uveitis affecting the pars plana which is between the colored part of the eye (iris) and the choroid. Uveitis can be associated with, for example, AIDS, ankylosing spondylitis, Behcet's syndrome, CMV retinitis, herpes zoster infection, histoplasmosis, injury, Kawasaki disease, psoriasis, reactive arthritis, rheumatoid arthritis, sarcoidosis, syphilis, toxoplasmosis, tuberculosis, and ulcerative colitis.

In some embodiments, treatment of uveitis that includes local delivery of an IL-17 inhibitor as described herein results in improvement in at least one sign or symptom of uveitis. Such symptoms are known in the art and include, for example, blurred vision; dark, floating spots in the vision; eye pain, redness of the eye; and sensitivity to light.

**Age-related macular degeneration AMD**

AMD involves breakdown of the macula and can be divided into a dry form affecting 90% of the AMD population and a more rapidly progressing and severe wet form involving blood vessel growth and leakage. It is the leading cause of vision loss in adults > 50 years old. There is no approved therapy for the dry form of AMD. Wet AMD is primarily treated with VEGF blockade, but a significant fraction of patients remain refractory. Therefore, there remains significant unmet medical need for treating AMD, particularly in the chronic disease setting.

IL-17A is upregulated in some advanced AMD patients with either geographic atrophy or neovascularization (Liu et al., J Transl Med 15:9:1-12, 2011). In an animal model of retinal degeneration mimicking dry AMD, IL-17 was upregulated in the retina.

The teachings provided herein provide methods of treating AMD by local administration of an IL-17 inhibitor, e.g., by topical or intravitreal administration. In some embodiments, treatment of a subject diagnosed with AMD results in an improvement in at least one sign or symptom of AMD or a slowing in the rate of progression of AMD.
In some embodiments, the IL-17 inhibitor is administered to a patient having AMD in a treatment regime that includes a second agent, e.g., a VEGF-A blocker, such as Lucentis® or Eylea®.

5 **Formulation and administration**

The IL-17 inhibitor (or pharmaceutical formulation comprising the IL-17 inhibitor) can be administered to the patient by any known delivery system and/or administration method. In some embodiments, the IL-17 inhibitor is administered to the patient by ocular, intraocular, intravitreal or subconjunctival injection.

IL-17 inhibitor compositions described herein can be prepared and administered using methods known in the art. In general, the IL-17 inhibitor composition is administered as an ophthalmic formulation, e.g., in a formulation suitable for intravitreal administration or in a formulation suitable for topical administration. The methods can comprise administration of the IL-17 inhibitor composition and an ophthalmically acceptable carrier. In some embodiments, the ophthalmic formulation is a liquid, semi-solid, insert, film, microparticle, or nanoparticle.

In some embodiments, the formulation is a liquid formulation comprising a polymer. Such a polymer can be used to improve the bioavailability, raise viscosity, or reduce drainage from the eye of a liquid formulation. Suitable polymers include, but are not limited to, those described in Wagh et al. (Asian J Pharm, 2:12-17, 2008). In non-limiting examples, the polymer is sodium hyaluronate, chitosan, a cyclodextrin (e.g., hydroxypropyl -P-cyclodextrin), polygalactronic acid, xylol glucan, xanthan gum, gellan gum, a thiomer, a poly(ortho ester) (e.g., Einmahl, Adv Drug Deliv Rev 53:45-73, 2001), or a tamarind seed polysaccharide (e.g., Ghelardi et al., Antimicrob Agents Chemother 48:3396-3401, 2004). In some embodiments, a formulation comprising an IL-17 inhibitor composition for ophthalmic delivery can comprise one or more of surfactants, adjuvants, buffers, antioxidants, tonicity adjusters, preservatives (e.g., EDTA, BAK (benzalkonium chloride), sodium chlorite, sodium perborate, polyquaterium-1), thickeners or viscosity modifiers (e.g., carboxymethyl cellulose, hydroxymethyl cellulose, polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose, hydroxypropyl-guar, hyaluronic acid, and hydroxypropyl cellulose) and the like. Additives in the formulation may include, but are not limited to, sodium chloride, sodium bicarbonate, sorbic acid, methyl paraben, propyl paraben, chlorhexidine, castor oil, and sodium perborate.
In some embodiments, purified or deionized water is used in the composition. The pH can be adjusted by adding any physiologically and ophthalmically acceptable pH adjusting acids, bases or buffers to within the range of about 5.0 to 8.5, e.g., pH 7.0, pH 7.3, pH 7.4, or pH 7.5. Ophthalmically acceptable examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, trishydroxymethylamino-methane, and the like. Examples of salts and buffers that can be used in a formulation include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

In some embodiments, the osmotic pressure of the ophthalmic composition may be from about 10 milliosmolar (mOsM) to about 400 mOsM, for example, 200 to 400 mOsM, or 220 to 370 mOsM. Generally, the osmotic pressure can be adjusted using physiologically and ophthalmically acceptable salts or excipients. In some embodiments, sodium chloride is included in a formulation, for example, sodium chloride is present in a formulation in a concentration ranging from 0.01% to 1% by weight, or from 0.05% to 0.45% by weight, based on the total weight of the composition. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the desired range. In some embodiments, a sugar such as mannitol, dextrose, sorbitol, glucose and the like is also used to adjust osmolality.

In some embodiments, the methods involve forming or supplying a depot of the agent in contact with the external surface of the eye. A depot refers to a source of agent that is not rapidly removed by tears or other eye clearance mechanisms. This allows for continued, sustained high concentrations of agent be present in the fluid on the external surface of the eye by a single application. In some embodiments, the depot can remain for up to eight hours or more. In some embodiments, the ophthalmic depot formulation includes, but is not limited to, aqueous polymeric suspensions, ointments, and solid inserts.

In some embodiments, a semi-solid composition is a liquid formulation that increases in viscosity upon application to the eye, typically due to the presence of a polymer in the liquid formulation for which an increase is viscosity occurs with a change in temperature, pH, or
electrolyte concentration. The polymer can be, for example, cellulose acetate phthalate, polyacrylic acid, gellan gum, hyaluronase, chitosan, salts of alginic acid (e.g., sodium alginate), or a block copolymer of ethylene oxide and propylene oxide (e.g., Pluronic®, BASF; poloxamer). In some embodiment, the polyacrylic acid is crosslinked acrylic acid (e.g., Carbopol®). In some embodiments, the semi-solid composition comprises a mixture of carbopol and a block copolymer of ethylene oxide and propylene oxide; a mixture of methyl cellulose and hydroxyethyl cellulose; or a mixture of polyethylene glycol and a block copolymer of ethylene oxide and propylene oxide.

In some embodiments, the IL-17 inhibitor containing ophthalmic formulation is an ointment or gel. In some embodiment, the ophthalmic formulation is an oil-based delivery vehicle. For example, the formulation can comprises a petroleum or lanolin base to which the IL-17 inhibitor composition is added (for example at 0.1 to 2%), and excipients. Common bases can include, but are not limited to, mineral oil, petrolatum and combinations thereof. In some embodiments, the ointment is applied as a ribbon onto the lower eyelid.

In some cases, the ophthalmic composition is an ophthalmic insert. For example, the ophthalmic insert is biologically inert, soft, bio-erodible, viscoelastic, stable to sterilization after exposure to therapeutic agents, resistant to infections from airborne bacteria, bio-erodible, biocompatible, and/or viscoelastic. In some embodiments, the insert comprises an ophthalmically acceptable matrix, e.g., a polymer matrix. The matrix is typically a polymer and the IL-17 inhibitor composition is dispersed within the matrix or bonded to the polymer matrix. In some embodiments, the agent is slowly released from the matrix through dissolution or hydrolysis of a covalent bond. In some embodiments, the polymer is bioerodible (soluble) and the dissolution rate thereof can control the release rate of the agent dispersed therein. In another form, the polymer matrix is a biodegradable polymer that breaks down such as by hydrolysis to thereby release the agent bonded thereto or dispersed therein. In further embodiments, the matrix and agent can be surrounded with an additional polymeric coating to further control release. In some embodiments, the insert comprises a biodegradable polymer such as polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacrylate, polyurethane, a nylon, or poly(dl-lactide-co-glycolide) (PLGA), or a copolymer of any of these. In some cases, the agent is dispersed into the matrix material or dispersed amongst the monomer composition used to make the matrix material prior to polymerization. In some embodiments, the amount of agent is from
about 0.1 to about 50%, or from about 2 to about 20%. The biodegradable or bioerodible polymer matrix can be used so that the spent insert does not have to be removed from the eye. As the biodegradable or bioerodible polymer is degraded or dissolved, the agent is released.

In further embodiments, the ophthalmic insert comprises a polymer, including, but are not limited to, those described in Wagh, et al. (Asian J Pharm, 2:12-17, 2008). In some embodiments, the insert comprises a polymer selected from poly(vinylpyrrolidone) (PVP), an acrylate or methacrylate polymer or copolymer (e.g., Eudragit® family of polymers from Rohm or Degussa), hydroxymethyl cellulose, polyacrylic acid, poly(amidoamine) dendrimers, poly(dimethylsiloxane), polyethylene oxide, poly(lactide-co-glycolide), poly(2-hydroxyethylmethacrylate), polyvinyl alcohol), or poly(propylene fumarate). In some embodiments, the insert comprises Gelfoam®. In some embodiments, the insert is a polyacrylic acid of 450 kDa-cysteine conjugate.

The insert can comprise a core that contains the IL-17 inhibitor composition and an outer tube (e.g., as described in U.S. Patent Pub. No. 20040009222). In some cases, the outer tube can be permeable, semi-permeable, or impermeable to the drug. In some embodiments, the core includes a polymer matrix that does not have a significant effect on the rate of IL-17 inhibitor composition release. In some cases, the outer tube, the polymer matrix of the core, or both is bioerodible. The co-extruded product can be segmented into drug delivery devices. In some embodiments, the device is uncoated so that the respective ends are open, or the device is coated with, for example, a layer that is permeable to the IL-17 inhibitor composition, semi-permeable to the IL-17 inhibitor composition, or bioerodible. In certain embodiments, the IL-17 inhibitor composition and at least one polymer are admixed in powder form.

In some embodiments, the ophthalmic composition is an ophthalmic film. Polymers suitable for such films include, but are not limited to, those described in Wagh, et al. (supra). In some embodiments, the film is a soft-contact lens, for example, a lens composed of copolymers of N,N-diethylacrylamide and methacrylic acid crosslinked with ethyleneglycol dimethacrylate.

In certain embodiments, the IL-17 inhibitor is in an insert that is in a tubular form, and may be segmented.

In some embodiments, the IL-17 inhibitor composition is formulated in a therapeutically effective amount, coated by or dispersed in a polymer matrix, such that the IL-17 inhibitor composition is in granular or particulate form. In some embodiments, the IL-17 inhibitor
composition is released from the formulation as drug from the granules dissolves into or within the matrix, diffuses through the matrix, and is released into the surrounding physiological fluid or substrate, e.g., the vitreous. In some embodiments, the rate of release is limited primarily by the rate of dissolution of the IL-17 inhibitor composition from the granules/particles into the matrix; the steps of diffusion through the matrix and dispersion into the surrounding fluid are primarily not release-rate-limiting. In certain embodiments, the polymer matrix is non-bioerodible, while in other embodiments it is bioerodible. Exemplary non-bioerodible polymer matrices can be formed from polyurethane, polysilicone, poly(ethylene-co-vinyl acetate) (EVA), polyvinyl alcohol, and derivatives and copolymers thereof. Exemplary bioerodible polymer matrices can be formed from polyanhydride, polylactic acid, polyglycolic acid, polyorthoester, polyalkylcyanoacrylate, and derivatives and copolymers thereof.

In some cases, the IL-17 inhibitor composition is formulated in a collagenous material. For example, the collagenous material can be a soluble ophthalmic drug insert (e.g., a polymeric oval film that can be introduced in the upper conjunctival sac for drug delivery; an elliptical insert such as OCUSERT® (pilocarpine ocular therapeutic system, developed by Alza Corporation) which is made of ethylene vinyl acetate; Lacrisert®, a rod shaped insert made of cellulose; New Ophthalmic Drug Delivery Systems (NODS), made of poly(vinyl alcohol); or inserts such as those described in Fabrizio (Adv Drug Deliv Rev 16: 95-106, 1998). In some cases, the insert comprises collagen, gelatin, or a polymer, wherein the polymer is selected from polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacrylate, polyurethane, a nylon, poly(dl-lactide-co-glycolide) (PLGA), or a copolymer of any of these. In some cases, the insert is implanted under the upper eyelid. In some cases, the insert is implanted in the posterior segment of the eye, in the choroidal space, or in the sclera. In some embodiments, the insert is implanted intravitreally or sub-retinally. In some embodiments, the insert is injected sub-retinally. Methods of administration and techniques for their preparation are set forth in Remington's: The Practice of Science of Pharmacy, 20th edition (Lippincott Williams & Wilkins, 2006), which is incorporated herein by reference in its entirety.

In other embodiments, an insert containing an IL-17 inhibitor composition provides a sustained release of the agent to the vitreous of the eye. As used herein, "sustained release" means that the composition releases the agent over an extended period of time in a controlled fashion. In some embodiments, the insert releases the agent at a rate such that the aqueous agent
concentration remains less than the vitreous agent concentration during the release. In some embodiments, the aqueous agent concentration is from about 0.002 µg/mL to about 0.01 µg/mL or from about 0.01 µg/mL, to about 0.05 µg/mL, or less than about 0.05 µg/mL. In some embodiments, the agent is released at a rate of about 1 µg/day to about 50 µg/day, or from about 1 µg/day to about 10 µg/day. In some embodiments, the insert further comprises an additional therapeutic agent, as detailed above, e.g., fluocinolone acetonide (such as that found in the ophthalmic insert Retisert®).

In some embodiments, the ophthalmic composition comprises microspheres or nanoparticles. In some embodiment, the microspheres comprise gelatin. In some embodiments, the microspheres are injected to the posterior segment of the eye, in the choroidal space, in the sclera, intravitreally or sub-retinally. In some embodiments, the microspheres or nanoparticles comprises a polymer including, but not limited to, those described in Wagh, et al. (supra). In some embodiments, the polymer is chitosan, a polycarboxylic acid such as polyacrylic acid, albumin particles, hyaluronic acid esters, polyitaconic acid, poly(butyl)cyanoacrylate, polycaprolactone, poly(isobutyl)caprolactone, poly(lactic acid-co-glycolic acid), or poly(lactic acid). In some embodiments, the microspheres or nanoparticles comprise solid lipid particles.

In some embodiments, an IL-17 inhibitor composition comprises an ion-exchange resin. In some embodiments, the ion-exchange resin is an inorganic zeolite or synthetic organic resin. In some embodiments, the ion-exchange resin includes, but is not limited to, those described in Wagh, et al., supra, which is incorporated herein by reference in its entirety. In some embodiments, the ion-exchange resin is a partially neutralized polyacrylic acid.

An IL-17 inhibitor composition can be provided in an aqueous polymeric suspension. In some embodiments, the IL-17 inhibitor composition or a polymeric suspending agent is suspended in an aqueous medium (e.g., having the properties as described above). Examples of polymeric suspending agents include, but are not limited to, dextrans, polyethylene glycols, polyvinylpyrrolidone, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose, and carboxy-containing polymers such as polymers or copolymers of acrylic acid, as well as other polymeric demulcents. In some embodiments, the polymeric suspending agent is a water swellable, water insoluble polymer, especially a crosslinked carboxy-containing polymer. In some embodiments, the polymeric suspending agent comprises from at least about 90% to about 99.9%, or from about 95% to about 99.9%, by weight based on the total weight of
monomers present, of one or more carboxy-containing monoethylenically unsaturated monomers. In some embodiments, the carboxy-containing monoethylenically unsaturated monomer includes acrylic acid, methacrylic acid, ethacrylic acid, methylacrylic acid (crotonic acid), cis-α,α-methylene-α-methylcrotonic acid (angelic acid), trans-a-methylene-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α,α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), and umbellic acid (p-hydroxycoumaric acid). In some embodiments, the polymer is crosslinked by a polyfunctional crosslinking agent (e.g., a difunctional crosslinking agent). In some embodiments, the crosslinking agent is contained in an amount of from about 0.01% to about 5%, or from about 0.1% to about 5.0%, or from about 0.2% to about 1%, based on the total weight of monomers present. In some embodiments, the crosslinking agents are nonpolyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide; polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, e.g., alkenyl ether groupings containing terminal H₂C=C groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000 Da, such as insoluble diacrylates and polyacrylates and methacrylates of diols and polyols, diisocyanate hydroxyalkyl acrylate or methacrylate reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like.

In some embodiments, the crosslinked polymers are made from a carboxy-containing monoethylenically unsaturated monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. In some embodiments, the polymers are ones in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxy-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomer or monomers containing only physiologically and ophthalmically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethylmethacrylate, 3-
hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like (e.g., Mueller et al. U.S. Pat. No. 4,548,990). In some embodiments, the polymers include polycarbophil (Noveon AA-1), Carbopol®, and DuraSite®. In some embodiments, the crosslinked polymers are prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 \( \mu \text{m} \) in equivalent spherical diameter. In some embodiments, the average dry particle size is from about 1 to about 30 \( \mu \text{m} \), or from about 3 to about 20 \( \mu \text{m} \) in equivalent spherical diameter. In some embodiments, the polymer particles are obtained by mechanically milling larger polymer particles. In further embodiments, such polymers will have a molecular weight from about 250,000 to about 4,000,000 Da, and from 3,000,000,000 to 4,000,000,000 Da. In other embodiments, the particles of crosslinked polymer are monodisperse, meaning that they have a particle size distribution such that at least about 80%, about 90% or about 95%, of the particles fall within a \( \mu \text{m} \) band of major particle size distribution. In further embodiments, the monodisperse particle size means that there is no more than about 20%, about 10%, or about 5% particles of a size below \( \mu \text{m} \). In some embodiments, the aqueous polymeric suspension comprises from about 0.05 to about 1%, from about 0.1 to about 0.5%, or from about 0.1 to about 0.5%, of the agent and from about 0.1 to about 10%, from about 0.5 to about 6.5%, from about 0.5 to about 2.0%, from about 0.5% to about 1.2%, from about 0.6 to about 0.9%, or from about 0.6 to about 0.8% of a polymeric suspending agent. Although referred to in the singular, it should be understood that one or more species of polymeric suspending agent can be used with the total amount falling within the stated ranges. In one embodiment, the amount of insoluble lightly crosslinked polymer particles, the pH, and the osmotic pressure can be correlated with each other and with the degree of crosslinking to give a composition having a viscosity in the range of from about 500 to about 100,000 centipoise, and preferably from about 1,000 to about 30,000 or about 1,000 to about 10,000 centipoise, as measured at room temperature (about 25°C.) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. In some embodiments, the viscosity is from about 10 to about 400 centipoise, from about 10 to about 200 centipoises or from about 10 to about 25 centipoise.

In some embodiments, the aqueous polymeric suspensions may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. In some embodiments, they may be formulated so that there is
increased gelation upon contact with tear fluid. For instance, when a formulation containing DuraSite® or other similar polyacrylic acid-type polymer is administered to the eye at a pH of less than about 6.7, the polymer may swell upon contact with tear fluid since it has a higher pH (around 7). This gelation or increase in gelation may lead to entrapment of the suspended particles, thereby extending the residence time of the composition in the eye. In some embodiments, the agent is released slowly as the suspended particles dissolve over time. In some embodiments, this delivery route increases patient comfort and increased agent contact time with the eye tissues, thereby increasing the extent of drug absorption and duration of action of the formulation in the eye. The agents contained in these drug delivery systems will be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present.

In some embodiments, the IL-17 inhibitor composition is formulated for topical administration, e.g., to the eye. The topical formulation can be a liquid formulation or semi-solid, for example, a topical formulation can include an aqueous solution, an aqueous suspension, an ointment or a gel. An ophthalmic IL-17 inhibitor formulation can be topically applied to the front of the eye, under the upper eyelid, on the lower eyelid and in the cul-de-sac. Typically, the ophthalmic formulation is sterile. An IL-17 inhibitor ophthalmic formulation can contain one or more pharmaceutical excipients suitable for the preparation of ophthalmic formulations.

Examples of such excipients are preserving agents, buffering agents, chelating agents, antioxidant agents and salts for regulating the osmotic pressure. Ophthalmic formulations, including both ointments and suspensions, typically have a viscosity that is suited for the selected route of administration. In some embodiments, the ophthalmic formulation has a viscosity of from about 5 to 30,000 centipoise, e.g., from about 1,000 to about 30,000 centipoise, or from about 5 to 50 centipoise, depending on the type of formulation and intended delivery method.

In some embodiments, local ocular treatment includes administering a pharmaceutical IL-17 inhibitor composition to a subject, the composition comprising the IL-17 inhibitor composition and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises, as the active ingredient, one or more of the agents above in combination with one or more pharmaceutically acceptable carriers (excipients). In making a
composition of the invention, the agent is typically mixed with an excipient, diluted by an
excipient or enclosed within such a carrier in a form such as those described above or, for
example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it
can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the
active ingredient. The formulations can be in the form of tablets, pills, powders, lozenges,
sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a
liquid medium), ointments containing, for example, up to 10% by weight of the active
compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged
powders.

In preparing a formulation, the IL-17 inhibitor composition can be milled to provide the
appropriate particle size prior to combining with the other ingredients. If the IL-17 inhibitor
composition is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If
the agent is substantially water soluble, the particle size can be adjusted by milling to provide a
substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol,
mannitol, starches, gum acacia, calcium phosphate, alginites, tragacanth, gelatin, calcium
silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl
cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium
stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents
such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The
compositions can be formulated so as to provide quick, sustained or delayed release of the active
ingredient after administration to the patient by employing procedures known in the art.

An IL-17 inhibitor composition can be formulated in a unit dosage form, each dosage
containing from about 5 to about 1000 mg (1 g), for example, about 100 to about 500 mg, of the
agent. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages
for human subjects and other mammals, each unit containing a predetermined quantity of active
material calculated to produce the desired therapeutic effect, in association with a suitable
pharmaceutical excipient.

An IL-17 inhibitor composition can be effective over a wide dosage range and is
generally administered in a pharmaceutically effective amount. It will be understood by those in
the art that the amount of the agent actually administered is typically determined by a physician,
according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient’s symptoms, and the like.

The amount and frequency of an IL-17 inhibitor composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated, e.g., uveitis or other IL-17 associated disorder of the eye, as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The therapeutic dosage of an IL-17 inhibitor composition agents can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of an agent in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the agents can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

EQUIVALENTS

All technical features can be individually combined in all possible combinations of such features.
The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein.

EXAMPLES

The following non-limiting examples further illustrate embodiments of the inventions described herein.

Example 1: In vivo treatment of uveitis with an IL-17 inhibitor

Experiments were conducted to determine whether local delivery of an IL-17 inhibitor would be effective for treatment of uveitis. Experiments were designed by the inventors and animal models generated and treated at Iris Pharma (La Gaude, France). Briefly, a rat model of autoimmune uveitis (experimental autoimmune uveitis; EAU) was generated by administering a single injection of S-antigen into the footpad of young female Lewis rats. In this model, disease onset is observed 9–12 days after immunization, and the peak of the disease occurs between 16 and 18 days after induction. The model was validated when 60% of the eyes from the vehicle group exhibited inflammation.

Blinded compounds that contained an IL-17 inhibitor, an IL-6 inhibitor, an IL-1 inhibitor, and a vehicle only control were administered by intravitreal injection (5µl/eye, both eyes were treated) into the experimental animals at day 7 and if endpoints were not reached by day 14, a second treatment was administered at day 14 after initiating induction of uveitis. The exception was for the positive control (cyclosporine A at 25 mg/kg), which was delivered orally once daily starting on day 7 after induction. Ocular examinations were performed using a slit lamp at baseline, then daily from day 12 to the endpoint to assess inflammation. At the endpoint The in-life phase of the experiment was stopped on day 14 when animals from the vehicle control group showed a mean severity score of 4.3 ± 1.7 and 100% of their eyes developed inflammatory signs. Animals were then sacrificed and histology of the eyeballs, focusing on the uvea, was performed, examining for signs of immune infiltration and tissue damage.

Intravitreal administration of the IL-1 inhibitor or the IL-6 inhibitor did not reduce intraocular inflammation compared with the vehicle group. Animals receiving the IL-17 inhibitor had reduced the intraocular inflammation compared with the vehicle group.
Consistent with the clinical signs, inflammatory cell infiltration was not reduced as assessed in histological preparations for animals treated with the IL-1 inhibitor or the IL-6 inhibitor. Inflammatory cell infiltration was reduced for animals treated with the IL-17 inhibitor (Fig. 1). Accordingly, locally administered anti-IL17 mAb reduced disease severity as measured by both clinical score and histology score compared to the vehicle control. In contrast, IL-6 blockade is efficacious in the EAU model when administered systemically, but not when administered IVT (Yoshimura et al., Rheumatology 48:347-54, 2009).

In these experiments, no significant decrease in disease incidence or clinical score was observed in animals locally treated with an IL-6 inhibitor or an IL-1 inhibitor. However, animals treated with an IL-17 inhibitor exhibited a significant decrease in both disease incidence and clinical score by day 12 of treatment. The improvement in uveitis was greater in animals treated using systemic cyclosporine.

These data demonstrate that effectiveness in systemic treatment of uveitis with an agent does not predict effectiveness for local treatment. The data also demonstrate that local administration of an IL-17 inhibitor can be useful for treating uveitis.

**Example 2: Treatment of uveitis with systemic and local treatment**

To determine whether combined treatment of uveitis using a systemic treatment such as with a corticosteroid, and a local treatment with IL-17 results in a synergistic effect, experiments such as those described in Example 1 are performed. In these experiments, animals are treated with vehicle control, locally administered IL-17, systemically administered cyclosporine A, or both local IL-17 and systemic cyclosporine A. Analysis is as in Example 1.

Other embodiments are within the scope of the following claims.
What is claimed is:

1. An IL-17 inhibitor formulated for local delivery for use in treating an ocular disease.

2. The IL-17 inhibitor of claim 1, wherein the ocular disease treated is uveitis or AMD.

3. The IL-17 inhibitor of claim 1, wherein the IL-17 inhibitor is an antibody that can specifically bind an IL-17.

4. The IL-17 inhibitor of claim 1, wherein the IL-17 inhibitor is formulated for intravitreal administration to the eye.

5. The IL-17 inhibitor of claim 1, wherein the IL-17 inhibitor is formulated for topical administration to the eye.

6. A method of treating an ocular disease in a subject, the method comprising administering a therapeutically effective amount of an IL-17 inhibitor to an affected eye of a subject.

7. The method of claim 6, wherein the ocular disease is uveitis or AMD.

8. The method of claim 6, wherein the subject is further treated systemically with a drug that is not a direct IL-17 inhibitor.

9. The method of any one of claims 6 to 8, wherein the IL-17 inhibitor is an antibody that can specifically bind an IL-17.

10. The method of any one of claims 6 to 9, wherein the IL-17 is administered intravitreally.
11. The method of any one of claims 6 to 9, wherein the IL-17 is administered topically to the eye.

12. The method of any one of claims 6 to 11, further comprising administering a systemic drug to the subject.

13. The method of claim 12, wherein the systemic drug is cyclosporine A.