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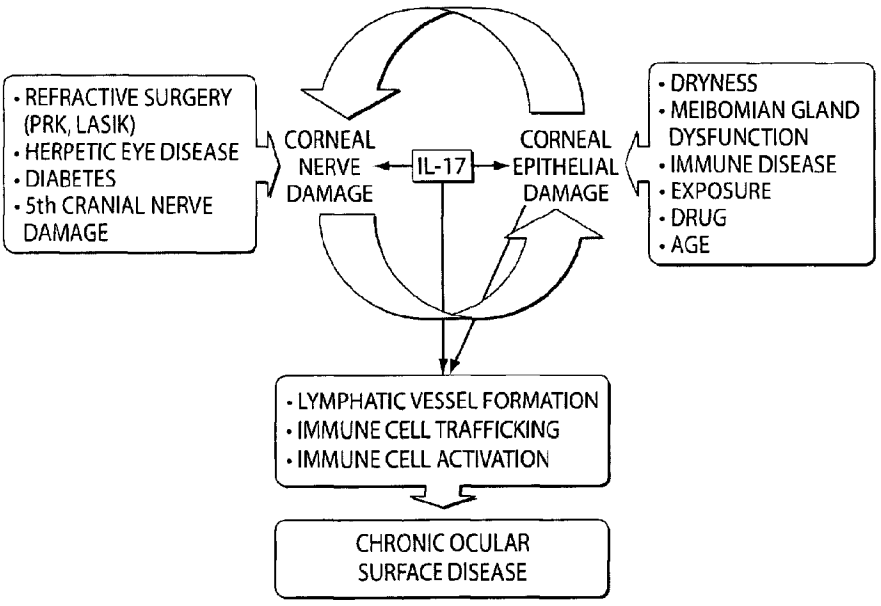
(72) Inventeurs/Inventors:
DANA, REZA, US;
CHAUHAN, SUNIL, US

(73) Propriétaire/Owner:
THE SCHEPENS EYE RESEARCH INSTITUTE, INC., US

(74) Agent: MBM INTELLECTUAL PROPERTY LAW LLP

(54) Titre : COMPOSITIONS THERAPEUTIQUES UTILISEES POUR LE TRAITEMENT DES AFFECTIONS INFLAMMATOIRES OCULAIRES

(54) Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF OCULAR INFLAMMATORY DISORDERS



(57) Abrégé/Abstract:
The invention comprises a composition with means to inhibit the function of the inflammatory cytokine IL-17 and methods for using this composition to treat IL-17-mediated ocular inflammatory disorders. The invention also discloses devices for delivering this composition to the eye.

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(71) Applicant *(for all designated States except US)*: **SCHEPENS EYE RESEARCH INSTITUTE** [US/US]; 20 Staniford Street, Boston, MA 02114-2500 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DANA, Reza** [US/US]; 165 Pleasant Street, Cambridge, MA 02139 (US). **CHAUHAN, Sunil** [IN/US]; 85 Mt. Vernon Street, Apt. #4, Somerville, MA 02145 (US).

(74) Agents: **BEATTIE, Ingrid A.** et al.; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo PC, One Financial Center, Boston, MA 02111 (US).

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(54) Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF OCULAR INFLAMMATORY DISORDERS

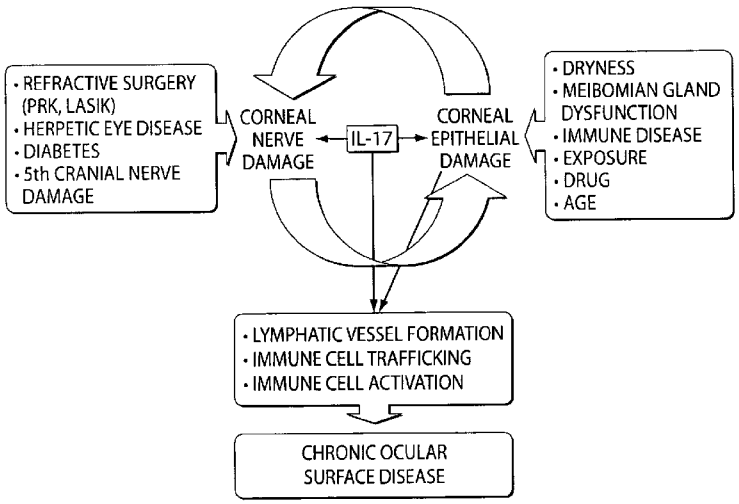


Fig. 13

(57) Abstract: The invention comprises a composition with means to inhibit the function of the inflammatory cytokine IL-17 and methods for using this composition to treat IL-17-mediated ocular inflammatory disorders. The invention also discloses devices for delivering this composition to the eye.

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THERAPEUTIC COMPOSITIONS FOR TREATMENT OF OCULAR INFLAMMATORY DISORDERS

[01] Deleted.

FIELD OF THE INVENTION

[02] This invention relates generally to the field of ophthalmology.

BACKGROUND OF THE INVENTION

[03] Ocular surface inflammatory disorders are one of the major causes of visual impairments. Dry Eye Syndrome (DES), which is also known as *keratoconjunctivitis sicca,* is a predominant ocular surface inflammatory disorder. Current knowledge of the etiology and pathogenesis of ocular surface inflammatory disorders remains inadequate and current treatments provide only temporary and incomplete symptomatic relief.

SUMMARY OF THE INVENTION

[04] The invention comprises a method for inhibiting or reducing the severity of an IL-17-mediated ocular surface inflammatory disorder by locally administering to an eye of a subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine such as binding of an inflammatory IL-17 cytokine to an IL-17 receptor or other elements of pro-inflammatory signaling pathways. The claimed compositions and methods fulfill a need for a treatment of an IL-17-mediated ocular surface inflammatory disorders that not only completely addresses the symptoms of this condition, but also affects the underlying biological mechanism. The ability of the methods described herein to target molecular signaling pathways that lead to ocular surface inflammatory disorders provides a long-term solution for treating these common, yet, complex conditions.

[05] In a preferred embodiment, the composition of the claimed invention inhibits the activity of IL-17A or IL-17F. Alternatively, the composition of the claimed invention inhibits the activity of IL-17A and IL-17F. In another preferred embodiment the composition of the claimed invention inhibits the activity of IL-17RA or IL-17RC. Alternatively, the composition of the claimed invention inhibits the activity of IL-17RA a

IL-17-mediated ocular surface inflammatory disorders of the invention comprise penetrating keratoplasty, corneal transplantation, lamellar or partial thickness transplantation, selective endothelial transplantation, corneal neovascularization, keratoprosthesis surgery, corneal ocular surface inflammatory conditions, conjunctival scarring disorders, autoimmune conditions, Pemphigoid syndrome, Stevens-Johnson syndrome, allergy, severe allergic (atopic) eye disease, conjunctivitis, and microbial keratitis. IL-17-mediated ocular surface inflammatory disorders comprise severe allergic (atopic) eye disease. Preferably, IL-17-mediated ocular surface inflammatory disorders do not comprise uveitis, intraocular conditions, or inflammation of interior tissues of the eye.

[06] In one preferred embodiment of the invention, the IL-17-mediated ocular surface inflammatory disorder is Dry Eye Syndrome (DES). Synonyms and related disorders of DES include, but are not limited to, keratoconjunctivitis sicca (KCS), Sjögren syndrome (SS), Sjögren syndrome associated keratoconjunctivitis sicca, non-Sjögren syndrome associated keratoconjunctivitis sicca, keratitis sicca, sicca syndrome, xerophthalmia, tear film disorder, decreased tear production, aqueous tear deficiency (ATD), meibomian gland dysfunction (MGD), and evaporative loss. The subject is identified as suffering from DES or a related disorder by detecting a sign or symptom selected from the group consisting of dry, scratchy, stingy, itchy, burning or pressured sensations, irritation, pain, redness, inflammation, discharge, and excessive eye watering. Alternatively, a subject is identified as suffering from DES or a related disorder if their tear composition is insufficient for proper eye tissue lubrication. The method of therapy inhibits or reduces the severity of at least one of these signs or symptoms.

[07] Dry eye is a multifactorial disorder of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (emp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes. *CLAO J* 1995;21:221-2). For a more detailed definition, see The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. Ocular Surface. 2007 Apr;5(2):75-92. The method of therapy inhibits or reduces the severity of at least one of these signs or symptoms.

[08] The method comprises administration of a compound that inhibits binding of an inflammatory IL-17 cytokine to the IL-17 receptor complex. Preferred formulations are in the form of a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a contact

lens, a film, an emulsion, or a suspension. The formulations are administered topically, e.g., the composition is delivered and directly contacts the eye. The composition is present at a concentration of 0.01 - 50% (weight/volume). For example, the inhibitory composition is present at concentrations of 1% (weight/volume), 10% (weight/volume), 20% (weight/volume), 25% (weight/volume), 30% (weight/volume), 40% (weight/volume), 50% (weight/volume), or any percentage point in between. The method does not involve systemic administration or planned substantial dissemination of the composition to non-ocular tissue.

[09] Optionally, the composition further contains a pharmaceutically-acceptable carrier. Exemplary pharmaceutical carriers include, but are not limited to, compounds selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/hydroxypropyl methyl cellulose (HPMC), carbopol-methyl cellulose, a mucolytic agent, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum. In one embodiment, the mucolytic agent is N-acetyl cysteine.

[10] All polynucleotides and polypeptides of the invention are purified and/or isolated. As used herein, an "isolated" or "purified" nucleic acid molecule, polynucleotide, polypeptide, or protein, is substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. Purified compounds are at least 60% by weight (dry weight) the compound of interest. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight the compound of interest. Purity is measured by any appropriate standard method, for example, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

[11] A method for inhibiting or reducing the severity of Dry Eye Syndrome is also carried out by locally administering to an eye of a subject a composition comprising a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that inhibits or modifies the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an inflammatory interleukin-17 cytokine or any component of the IL-17 receptor complex.

[12] The composition may comprise a neutralizing or function-blocking antibody against IL-17 and/or a receptor complex. The neutralizing or function-blocking antibody against IL-17 may be a reformulated or humanized derivative of or bind to the epitope of human IL-17 affinity purified polyclonal antibody (Catalog # AF-317-NA, R&D Systems), human IL-17 allophycocyanin monoclonal antibody (clone 41802)(Catalog # IC3171A, R&D Systems), human IL-17 biotinylated affinity purified polyclonal antibody (Catalog # BAF317, R&D

Systems), human IL-17 monoclonal antibody (clone 41802)(Catalog # MAB3171, R&D Systems), human IL-17 monoclonal antibody (clone 41809)(Catalog # MAB317, R&D Systems), human IL-17 phycoerythrin monoclonal antibody (clone 41802)(Catalog # IC3171P, R&D Systems), mouse IL-17 affinity purified polyclonal antibody (Catalog # AF-421-NA, R&D Systems), mouse IL-17 biotinylated affinity purified polyclonal antibody (Catalog # BAF421, R&D Systems), mouse IL-17 monoclonal antibody (clone 50101)(Catalog # MAB721, R&D Systems), or mouse IL-17 monoclonal antibody (clone 50104)(Catalog # MAB421, R&D Systems). Preferably, the neutralizing or function-blocking antibody against IL-17 may be a reformulated or humanized derivative of or bind to the epitope of monoclonal anti-human IL-17 antibody, (Clone: 41809, Catalog # MAB317, R&D Systems), anti-human IL-17 antibody, polyclonal raised in Goat, (Catalog # AF-317-NA, R&D Systems), or recombinant human IL-17 R/Fc chimera (Catalog # 177-IR, R&D Systems).

[13] The neutralizing or function-blocking antibody against an IL-17 receptor (Il-17R) may be a reformulated or humanized derivative of or bind to the epitope of human IL-17R affinity purified polyclonal antibody (Catalog # AF177, R&D Systems), human IL-17R allophycocyanin monoclonal antibody (clone 133617)(Catalog # FAB177A, R&D Systems), human IL-17R biotinylated affinity purified polyclonal antibody (Catalog # BAF177, R&D Systems), human IL-17R fluorescein monoclonal antibody (clone 133617) (Catalog # FAB177F, R&D Systems), human IL-17R monoclonal antibody (clone 133617)(Catalog # MAB177, R&D Systems), human IL-17R monoclonal antibody (clone 133621)(Catalog # MAB1771, R&D Systems), human IL-17R phycoerythrin monoclonal antibody (clone 133617)(Catalog #FAB177P, R&D Systems), mouse IL-17R affinity purified polyclonal antibody (Catalog # AF448A, R&D Systems), mouse IL-17R biotinylated affinity purified polyclonal antibody (Catalog # BAF448, R&D Systems), or mouse IL-17R monoclonal antibody (clone 105828)(Catalog # MAB448, R&D Systems).

[14] The neutralizing or function-blocking antibody against an IL-17 may be a reformulated or humanized derivative of, or bind to the epitope of, one or more formats of mouse anti-IL-17A (SKU #s including but not limited to, 7172, 7173, 7175, 7177, 8171, 7371, 7971, and 7370, eBioscience) or mouse anti-IL-17F (SKU #s including, but not limited to, 7471 and 8471, eBioscience). The neutralizing or function-blocking antibody against an IL-17 may be a reformulated or humanized derivative of one or more formats of human anti-IL-17A (SKU #s including, but not limited to, 7178, 7179, 8179, 7176, 7976, and 7876 or human anti-IL-17F SKU #s including, but not limited to, 8479, eBioscience). Preferably, the

neutralizing or function-blocking antibody against an IL-17 may be a reformulated or humanized derivative of, or bind to the epitope of functional grade purified anti-human IL-17A antibody (Clone: eBio64CAP17, Catalog # 16-7178. eBioscience).

[15] Alternatively, the composition may comprise an intrabody that binds to the IL-17 receptor complex or any synthetic intermediate of IL-17 or the IL-17 receptor complex. The composition may alternatively, or in addition, comprise a soluble fragment of the IL-17 receptor complex which binds IL-17.

[16] Exemplary polypeptides include, but are not limited to, fusion and/or chimeric proteins capable of disrupting IL-17 function. Moreover, the composition comprises morpholino antisense oligonucleotides, microRNAs (miRNAs), short hairpin RNA (shRNA), or short interfering RNA (siRNA) to silence gene expression.

[17] Contemplated function-blocking antibodies targeted against an IL-17 cytokine or an IL-17 receptor are monoclonal or polyclonal. The contemplated antibody binds to one or more sequences within an IL-17 or IL-17 receptor polypeptide. The antibody is alternatively an intrabody. In some embodiments, the antibody comprises a single chain, a humanized, a recombinant, or a chimeric antibody. One or more compounds are directly or indirectly conjugated onto this antibody.

[18] Antagonists of IL-17 and/or its receptor complex are administered either simultaneously or sequentially with a secondary composition comprising one or more of the following: an antibiotic, an immunosuppressive composition, an anti-inflammatory composition, a growth factor, a steroid, a chemokine, or a chemokine receptor.

[19] The composition comprises microRNA molecules adapted for topical administration to ocular or adnexal tissues in order to silence gene expression. Exemplary miRNAs that bind to human IL-17R include, but are not limited to, miR-24 (SEQ ID NO:33), miR-378 (SEQ ID NO:34), and let-7g (SEQ ID NO:35).

[20] Small molecules are organic or inorganic. Exemplary organic small molecules include, but are not limited to, aliphatic hydrocarbons, alcohols, aldehydes, ketones, organic acids, esters, mono- and disaccharides, aromatic hydrocarbons, amino acids, and lipids. Exemplary inorganic small molecules comprise trace minerals, ions, free radicals, and metabolites. Alternatively, small molecule inhibitors can be synthetically engineered to consist of a fragment, or small portion, or a longer amino acid chain to fill a binding pocket of an enzyme. Typically small molecules are less than one kilodalton.

[21] In one embodiment of the invention, the composition comprises one or more antibiotic compositions to be used in combination with an antagonist of IL-17 function. The

antibiotic and IL-17 antagonist compositions are administered simultaneously or sequentially. Exemplary antibiotic compositions used for combination-therapy with antagonists of IL-17 function include but are not limited to, amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, tobramycin, teicoplanin, vancomycin, azithromycin, clarithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, amoxicillin, ampicillin, azlocillin, carbenicillin, clozacillin, dicloxacillin, flucozacillin, mezlocillin, nafcillin, penicillin, piperacillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, oflazacin, trovafloxacin, mafenide, sulfacetamide, sulfamethizole, sulfasalazine, sulfisoxazole, tetracycline, trimethoprim, cotrimoxazole, demeclocycline, soxycycline, minocycline, doxycycline, oxytetracycline, or tetracycline.

[22] The composition comprises an antagonist of an IL-17 cytokine or an IL-17 receptor complex, administered simultaneously or sequentially with a second immunosuppressive composition. The composition comprising an IL-17 or IL-17R antagonist is administered topically. The second immunosuppressive composition is administered topically or systemically.

[23] The immunosuppressive compound comprises cyclosporin A or analogs thereof a concentration of 0.05 - 4.0 % (mg/ml). Alternatively, or in addition, the immunosuppressive composition comprises a glucocorticoid, a cytostatic agent, an alkylating agent (nitrogen mustards/cyclophosphamide, nitrosoureas, platinum compounds), an antimetabolic agent (methotrexate, any folic acid analog, azathioprine, mercaptopurine, any purine analog, any pyrimidine analog, any inhibitor of protein synthesis), a cytotoxic antibiotic (dactinomycin, an anthracycline, mitomycin C, bleomycin, mithramycin), a polyclonal antibody (Atgam®, Thympglobuline®, any antibody against the antilymphocyte or antithymocyte antigens), a monoclonal antibody (OKT3®, any antibody against the T-cell receptor, any antibody against IL-2, basiliximab/Simulect®, declizumab/Zenapax®), Tacrolimus/Prograf™/FK506, Sirolimus/Rapamune™/Rapamycin, interferon beta, interferon gamma, an opioid, a TNFα binding protein, mycophenolate, or FTY720.

[24] The composition comprises a polynucleotide, a polypeptide, an antibody, or a small molecule that binds or modifies the function of IL-17 or IL-17R administered topically with a pharmaceutically appropriate carrier. Delivery methods for polynucleotide compositions include, but are not limited to, liposomes, receptor-mediated delivery systems, naked DNA, and engineered viral vectors such as herpes viruses, retroviruses, adenoviruses and adeno-associated viruses, among others. Polynucleotide compositions are administered topically

with a pharmaceutically acceptable liquid carrier, e.g., a liquid carrier, which is aqueous or partly aqueous. Alternatively, polynucleotide sequences within the composition are associated with a liposome (e.g., a cationic or anionic liposome).

[25] A number of methods have been developed for delivering short DNA or RNA sequences into cells; e.g., polynucleotide molecules can be contacted directly onto the tissue site, or modified polynucleotide molecules, designed to specifically target desired cell types (e.g., sequences linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface).

[26] A preferred approach uses a recombinant DNA construct in which the short polynucleotide sequence is placed under the control of a strong polymerase III or polymerase II promoter. The use of such a construct will result in the transcription of sufficient amounts of polynucleotide that will form complementary base pairs with the endogenous transcripts of nucleic acids of the invention and thereby prevent translation of endogenous mRNA transcripts. The invention encompasses the construction of a short polynucleotide using the complementary strand as a template. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an interfering RNA or precursor to a double stranded RNA molecule. Alternatively, the template for the short polynucleotide transcript is placed under the transcriptional control of a cell-type specific promoter or other regulatory element. Thus, diffusion or absorption of a topically administered composition beyond the intended ocular target tissue does not cause deleterious or systemic side effects. The vector remains episomal or becomes chromosomally integrated, as long as it can be transcribed to produce the desired polynucleotide.

[27] Vectors are constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian cells. Expression of the sequence encoding the short polynucleotide can be placed under the control of any promoter known in the art to act in mammalian, preferably human cells. Promoters are inducible or constitutive. Exemplary promoters include, but are not limited to: the SV40 early promoter region (Bernoist et al., Nature 290:304, 1981); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell, 22:787-797, 1988); the herpes thymidine kinase promoter (Wagner et al., Proc. Natl. Acad. Sci. USA, 78:1441, 1981); or the regulatory sequences of the metallothionein gene (Brinster et al., Nature, 296:39, 1988).

[28] Polypeptide compositions are associated with liposomes alone or in combination with receptor-mediated delivery systems, to enable transport across the plasma membrane.

Polypeptide compositions are soluble or membrane-bound. An exemplary receptor-mediated delivery system involves fusion of a low-density or very-low-density lipoprotein containing particle or vesicle to the low-density lipoprotein (LDL) receptor (LDLR) as observed with Hepatitis C Virus (HCV) infection and HCV-mediated drug delivery methods.

[29] Compositions comprise one or more extracellular or intracellular antibodies, also called intrabodies, raised against IL-17 or an IL-17 receptor complex. Extracellular antibodies are topically administered with a pharmacologically appropriate aqueous or non-aqueous carrier. Sequences encoding intracellular antibodies are subcloned into a viral or mammalian expression vector, packed in a lipophilic device to facilitate transport across the plasma membrane, and topically administered to eye tissue with a pharmacologically appropriate aqueous or non-aqueous carrier. Once inside the plasma membrane, host cell machinery transcribes, translates, and processes the intrabody code to generate an intracellular function-blocking antibody targeted against IL-17 or an IL-17 receptor complex. In the case of secreted molecules, intracellular antibodies prevent post-translational modification or secretion of the target protein. In the case of membrane-bound molecules, intracellular antibodies prevent intracellular signaling events upon receptor engagement by IL-17 cytokines.

[30] The composition comprises an antagonist of IL-17 and/or an IL-17 receptor complex function in combination with other inhibitory elements. Antagonists of IL-17 and/or an IL-17 receptor complex and other inhibitory elements are administered simultaneously or sequentially. In one embodiment, the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and an antagonist of tumor necrosis factor alpha (TNFα). Exemplary functional blockers of TNFα include, but are not limited to, recombinant and/or soluble TNFα receptors, monoclonal antibodies, and small molecule antagonists and/or inverse agonists. One or more commercially-available TNF-α blocking agents are reformulated for topical administration in this embodiment. Exemplary commercial TNF-α blocking agents used for reformulation include, but are not limited to, etanerept/Embrel™, infliximab/Remicade™, and adalimumab/Humira™. Alternatively, the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and antagonist(s) of one or more interleukin cytokines. Exemplary cytokines include, but are not limited to, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL-18, and IL-23. In another embodiment, the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and antagonist(s) of one or more member(s) of the vascular epithelial growth factor (VEGF) family composed of growth

factors and receptors (VEGFR). Exemplary members include, but are not limited to, VEGF-A, VEGF-C, VEGFR-2, and VEGFR-3. In another embodiment, the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and an antagonist of interferon-gamma. In another embodiment, the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and antagonist(s) of one or more chemokines and their receptors. Exemplary chemokines and receptors comprised by the composition of this embodiment include, but are not limited to, chemokine (C-C motif) receptor 1 (CCR1), chemokine (C-C motif) receptor 2 (CCR2), chemokine (C-C motif) receptor 5 (CCR5), chemokine (C-C motif) receptor 7 (CCR7), and chemokine (C-X-C motif) receptor 3 (CXCR3).

[31] In embodiments wherein the composition comprises an antagonist of IL-17 and/or IL-17 receptor function and a second composition, the respective doses of the IL-17 antagonist to the second composition is a ratio between 1:10 and 10:1 (mass/weight). Alternatively, the ratio is 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, or 9:1.

[32] The invention also comprises a contact lens device consisting of a composition that inhibits an activity of an inflammatory interleukin-17 cytokine and a pharmaceutically compatible polymer. This composition also comprises a combination of antagonists of IL-17 or IL-17 receptor function as well as secondary compositions. For example, the composition is incorporated into or coated onto said lens. The composition is either chemically bound or physically entrapped by the contact lens polymer. The contact lens is either hydrophobic or hydrophilic.

[33] The invention comprises a drug-delivery device consisting of a composition that inhibits an activity of an inflammatory interleukin-1 cytokine and a pharmaceutically compatible polymer. This composition also comprises a combination of antagonists of IL-17 or IL-17 receptor function as well as secondary compositions. For example, the composition is incorporated into or coated onto said polymer. The composition is either chemically bound or physically entrapped by the polymer. The polymer is either hydrophobic or hydrophilic. The polymer device comprises multiple physical arrangements. Exemplary physical forms of the polymer device include, but are not limited to, a film, a scaffold, a chamber, a sphere, a microsphere, a stent, or other structure. The polymer device has internal and external surfaces. The device has one or more internal chambers. These chambers contain one or more compositions. The device contains polymers of one or more chemically-differentiable monomers. The subunits or monomers of the device polymerize *in vitro* or *in vivo*.

[34] The invention comprises a device comprising a polymer and a bioactive composition incorporated into or onto said polymer, wherein said bioactive composition inhibits an

activity of an inflammatory interleukin-17 cytokine, and wherein said device is implanted or injected into an ocular surface tissue, an adnexal tissue in contact with an ocular surface tissue, a fluid-filled ocular or adnexal cavity, or an ocular or adnexal cavity.

[35] Exemplary mucoadhesive polyanionic natural or semi-synthethic polymers from which the device is formed include, but are not limited to, polygalacturonic acid, hyaluronic acid, carboxymethylamylose, carboxymethylchitin, chondroitin sulfate, heparin sulfate, and mesoglycan. In one embodiment, the device comprises a biocompatible polymer matrix that may optionally be biodegradable in whole or in part. A hydrogel is one example of a suitable polymer matrix material. Examples of materials which can form hydrogels include polylactic acid, polyglycolic acid, PLGA polymers, alginates and alginate derivatives, gelatin, collagen, agarose, natural and synthetic polysaccharides, polyamino acids such as polypeptides particularly poly(lysine), polyesters such as polyhydroxybutyrate and poly-.epsilon.-caprolactone, polyanhydrides; polyphosphazines, poly(vinyl alcohols), poly(alkylene oxides) particularly poly(ethylene oxides), poly(allylamines)(PAM), poly(acrylates), modified styrene polymers such as poly(4-aminomethylstyrene), pluronic polyols, polyoxamers, poly(uronic acids), poly(vinylpyrrolidone) and copolymers of the above, including graft copolymers. In another embodiment, the scaffolds may be fabricated from a variety of synthetic polymers and naturally-occurring polymers such as, but not limited to, collagen, fibrin, hyaluronic acid, agarose, and laminin-rich gels.

[36] One preferred material for the hydrogel is alginate or modified alginate material. Alginate molecules are comprised of (1-4)-linked β-D-mannuronic acid (M units) and α L-guluronic acid (G units) monomers which vary in proportion and sequential distribution along the polymer chain. Alginate polysaccharides are polyelectrolyte systems which have a strong affinity for divalent cations (e.g. Ca^{+2}, Mg^{+2}, Ba^{+2}) and form stable hydrogels when exposed to these molecules. See Martinsen A., et al., Biotech. & Bioeng., 33 (1989) 79-89.

[37] An embodiment of the invention utilizes an alginate or other polysaccharide of a lower molecular weight, preferably of size which, after dissolution, is at the renal threshold for clearance by humans. Polymeric devices are located topically or subcutaneously, though very superficially, wherein either a composition chemically bound or physically entrapped by the polymeric device or the device itself, degrades and must be cleared from the body. For a biodegradable polymeric device, it is preferred that the alginate or polysaccharide is reduced to a molecular weight of 1000 to 80,000 daltons, more preferably 1000 to 60,000 daltons, particularly preferably 1000 to 50,000 daltons. It is also useful to use an alginate material of

high guluronate content since the guluronate units, as opposed to the mannuronate units, provide sites for ionic crosslinking through divalent cations to gel the polymer.

[38] Internal and external surfaces optionally contain pores. Pores are either created prior to administration into a subject or result from the inclusion of pore-forming agents within the device that perforate surfaces upon administration to a subject. Exemplary pore forming agents include, but are not limited to, water soluble compounds such as inorganic salts and sugars. Pore forming agents are added as particulates and comprise between one and thirty percent (weight/weight of polymer). Pore size is sufficient for diffusion of proteins but not large enough cell migration into or out of the device.

[39] The device is administered topically, subconjunctively, or in the episcleral space, subcutaneously, or intraductally. Specifically, the device is placed on or just below the surface if an ocular tissue. Alternatively, the device is placed inside a tear duct or gland. The composition incorporated into or onto the polymer is released or diffuses from the device.

[40] The invention comprises a composition with variable physical and chemical forms; however, the composition is topically administered and contacts an eye directly. The composition is administered as a solid, a paste, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a film, an emulsion, or a suspension. Furthermore, the composition is incorporated into or coated onto a contact lens or drug delivery device, from which one or more molecules diffuse away from the lens or device or are released in a temporally-controlled manner. In this embodiment, the contact lens composition either remains on the ocular surface, e.g. if the lens is required for vision correction, or the contact lens dissolves as a function of time simultaneously releasing the composition into closely juxtaposed tissues. Similarly, the drug delivery device is optionally biodegradable or permanent in various embodiments.

[41] In one preferred embodiment, the invention comprises a composition with means to inhibit the transcription, transcript stability, translation, modification, localization, secretion, or receptor binding of IL-17. In one preferred embodiment, the composition is capable of binding to one or more regions of an IL-17 mRNA transcript or the IL-17 polypeptide. Alternatively, the composition is capable of binding to one or more regions of an IL-17 mRNA transcript or an IL-17 polypeptide selected from the group consisting of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. In another preferred embodiment, the composition is capable of binding to one or more regions of an IL-17A mRNA transcript or the IL-17F polypeptide.

[42] The composition comprises an antagonist or inverse agonist of a receptor for IL-17. IL-17 receptors comprise IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. Preferably

IL-17RA and IL-17RC are targeted by an antagonist or inverse agonist. In this embodiment an antagonist is defined as a binding partner, or ligand, of an IL-17R that inhibits the function of an agonist, IL-17, or inverse agonist by blocking its binding to the receptor. An inverse agonist is defined as a molecule which binds to the same IL-17R binding-site as an agonist, for instance, IL-17, but exerts the opposite pharmacological effect. The composition contains a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule that binds to a region of an IL-17R mRNA or polypeptide.

[43] In another preferred embodiment, the composition comprises a human recombinant IL-17R antagonist either in pure form, or as a component of a mixture. The human recombinant IL-17R antagonist is combined with balanced saline, carboxymethylcellulose (CMC), or hyaluronic acid (HA), or other vehicles prior to the composition contacting the ocular surface. Within these mixtures, the human recombinant IL-17R antagonist comprises at least 0.1%, 2.0%, 2.5%, 5%, 10% or at most 50% of the total volume administered. Purified is defined as the antagonist in the absence of unrelated polynucleotides, polypeptides, cellular organelles, or lipids. Purified defines a degree of sterility that is safe for administration to a human subject, e.g. lacking infectious or toxic agents.

[44] The invention provides a method of restoring or augmenting regulatory T-cell-mediated immune suppression in a subject with an IL-17-mediated ocular disease including administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, restoring or augmenting regulatory T-cell-mediated immune suppression. Alternatively, or in addition, the invention also provides a method of restoring or augmenting regulatory T-cell-mediated immune suppression in a subject with dry eye including administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby restoring or augmenting regulatory T-cell-mediated immune suppression. Alternatively, the subject has an ocular disorder.

[45] Furthermore, the invention provides a method of reducing Th17 cell abundance in an ocular, adnexal, or lymph tissue of a subject in need thereof including administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine. For example, a method of decreasing or inhibiting secretion of lymphangiogenesis-specific growth factors in an ocular or adnexal tissue of a subject with dry eye is carried out by administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby inhibiting lymphangiogenesis. In certain embodiments of the invention, the lymphangiogenesis-specific growth factors are VEGF-C, VEGF-D, a VEGF receptor, or a combination thereof. Moreover, the invention provides a method of decreasing

or inhibiting secretion of lymphangiogenesis-specific growth factors in an ocular or adnexal tissue of a subject with an IL-17-mediated ocular disease including administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby inhibiting lymphangiogenesis.

[46] Furthermore, the invention provides a method of reducing macrophage and monocyte cell abundance or concentration in an ocular, adnexal, or lymph tissue of a subject in need thereof including administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine.

[47] A method of reducing pathogenic immune cell abundance in an ocular, adnexal, or lymph tissue of a subject in need thereof includes administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine. As used herein, the term "pathogenic immune cell" is meant to describe any immune cell that exacerbates, induces, reduces the time to onset, or prolongs the appearance a sign or symptom of an ocular disease. Pathogenic immune cells in this context antagonize or decrease an IL-17 inhibiting activity of compositions of the invention.

[48] Pathogenic lymphatic vessel growth in an ocular, or adnexal tissue of a subject is inhibited or reduced by administering to the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine. Pathogenic lymphatic vessel growth encompasses lymphatic vessel growth that exacerbates, induces, reduces the time to onset, or prolongs the appearance a sign or symptom of an ocular disease. Moreover, pathogenic lymphatic vessel growth antagonizes or decreases an IL-17 inhibiting activity of compositions of the invention. Alternatively, or in addition, pathogenic lymphatic vessel growth occurs prior to, simultaneously with, or following the presentation of an IL-17-mediated ocular disease. Pathogenic lymphatic vessel growth includes the ability of lymphatic vessels to expand within or to invade corneal tissue or describes the potential and/or actual growth, expansion, elaboration, splitting, or remodeling of lymphatic vessels either within a corneal tissue or from a non-corneal tissue (such as the adjacent limbus) into corneal tissue. Alternatively, or in addition, pathogenic lymphatic vessel growth permits or induces the transport of immune cells, which encompasses the unidirectional or bidirectional movement or deposition of an immune cell between a corneal tissue and a non-corneal tissue, preferably, a lymph node or other sites in the lymphoid compartment. Exemplary immune cells is include, but are not limited to, T cells, B cells, dendritic cells, macrophages, monocytes, and natural killer (NK) cells.

[49] The invention also provides a method for reducing corneal nerve damage in a subject in need thereof, including the steps of: (a) identifying a subject with corneal nerve damage; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine, thereby enhancing corneal nerve regeneration, reducing the development of abnormalities in nerve morphology, and reducing corneal nerve damage.

[50] In certain embodiments of the above method, the subject is identified as having corneal nerve damage or loss that results from a congenital defect, disease, trauma, medical or surgical procedure. Alternatively, or in additional, the subject is identified as having corneal nerve damage or loss that results from neurotrophic keratitis, herpes simplex, zoster keratitis, diabetes mellitus, trigeminal nerve damage, orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), congenital defect, ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, peripheral neuropathy, or diabetic neuropathy.

[51] The invention provides a method for preventing corneal nerve damage in a subject in need thereof, including the steps of: (a) identifying the subject at risk of exposure to corneal nerve damage; and (b) locally administering to the cornea of the subject a composition that inhibits an activity of an inflammatory interleukin-17 cytokine prior to the exposure, thereby decreasing nerve degeneration, reducing the development of abnormalities in nerve morphology, and preventing damage corneal nerve damage.

[52] For example, the subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from disease, trauma, or a medical procedure. Alternatively, or in addition, the subject is identified as being at risk of exposure to corneal nerve damage or loss that could result from neurotrophic keratitis, herpes simplex, zoster keratitis, diabetes mellitus, trigeminal nerve damage, orbital or head surgery, head trauma, aneurysm, intracranial neurologic disease, keratorefractive procedures, photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), ocular surface disease, dry eye syndrome, a non-ophthalmic disorder, a non-ophthalmic procedure, peripheral neuropathy, or diabetic neuropathy.

[53] The above methods further include the step of identifying a subject with a sign or symptom of corneal nerve damage or loss. For example, a sign of corneal nerve damage or loss is a decrease of corneal innervation or sensation, a reduction in the number of nerve fibers or bundles innervating the cornea, death of neurons innervating the cornea, a decrease

or loss of neurotransmitter release, a decrease or loss of nerve growth factor release, abnormal tearing reflexes, abnormal blink reflexes, abnormal nerve morphology, appearance of abnormal nerve sprouts, abnormal tortuosity, increased bead-like nerve formations, thinning of nerve fiber bundles, or thickening of nerve fiber bundles. For example, a symptom of corneal nerve damage or loss is abnormal tear production or dryness, abnormal blinking, and difficulty or loss of ability to focus, decreased or lost visual acuity, or decreased or lost corneal sensitivity.

[54] Signs or symptoms of corneal damage or abnormal nerve morphology are detected, analyzed, examined, and evaluated using *in vivo* confocal microscopy (IVCM) of the central cornea or other imaging or diagnostic devices that allow for detection of corneal nerve damage. Exemplary devices for IVCM include, but are not limited to the Heidelberg Retina Tomograph 3 with the Rostock Cornea Module (HRT3/RCM) (Heidelberg Engineering GMBH) and the Confoscan 4 Confocal Microscope (Nidek, Inc.). In certain embodiments of the above methods, IVCM is used to detect, analyze, examine, and evaluate the form and number of nerve fibers in the various corneal layers, as well as to discriminate between parallel running, bifurcating, branching, and interconnecting nerve fiber bundles. Alternatively or in addition, IVCM is used to detect, analyze, examine, and evaluate changes in the total number of nerves, changes in the length of nerves, nerve density, the presence or absence of abnormal nerve sprouts, the presence or absence of abnormal nerve fiber tortuosity, changes in number or morphology of bead-like nerve formations, and thinning versus thickening of nerve fiber bundles. In one aspect of the methods of the invention, IVCM is used to detect, analyze, examine, and evaluate nerve regeneration. Alternatively, or in addition, IVCM is used to detect, analyze, examine, and evaluate nerve degeneration. For instance, IVCM has been used to show an average of 6-8 corneal nerve bundles per image within the subbasal area of healthy individuals and nerve regeneration in patients who experienced nerve damage as a result of photoreceptive keratectomy.

[55] In certain preferred embodiments, the above methods are performed on a corneal tissue.

[56] Deleted.

BRIEF DESCRIPTION OF THE DRAWINGS

[57] Table 1 is a summary of mRNAs comprised in the invention, their human target genes, amino acid sequences, and their sequence identifier numbers.

[58] Figure 1 is a series of graphs depicting flow cytometric dots demonstrating increased frequency of IL-17 producing CD4+ T cells in the draining lymph nodes of mice with DES compared to those of normal mice ($p=0.03$).

[59] Figure 2 is a graph showing the fold change in IL-17 expression in normal versus DES mice. Conjunctiva of mice with DES expresses approximately a 2.5-3 fold increase in IL-17 mRNA abundance compared to those of normal mice.

[60] Figure 3A-B is a pair of photographs of immunofluorescence showing that IL-17RAs are constitutively expressed on the epithelium of (A) cornea and (B) conjunctiva of both normal mice as well as mice with DES.

[61] Figure 4A is a schematic diagram of the experimental design for Figures 4B, 4C, and 4D.

[62] Figure 4B is a graph showing the CFS score on days 1-5 of either control or IL-17 Ab treated corneas. More than 50% reduction in the DES-clinical score was observed during induction as well as progression phase of the disease in mice treated with anti-IL-17 antibody compared to those treated with control antibody

[63] Figure 4C is a series of graphs depicting flow cytometric dots demonstrating that a decreased frequency of IL-17+CD4+ T cells was observed in the draining lymph nodes of anti-IL-17 antibody treated group as compared to those of the control-antibody treated group.

[64] Figure 4D is a graph of the fold change in IL-17 mRNA expression in the conjunctiva of normal versus either IL-17 or Control Ab-treated groups. Conjunctiva of mice treated with anti-IL-17 antibody showed decreased IL-17 mRNA expression than those of treated with control antibody.

[65] Figure 5 is the Oxford schema for grading corneal and conjunctival staining (*see*, Example 4).

[66] Figure 6 is an Ocular Surface Disease Index (OSDI) 12-item questionnaire.

[67] Figure 7 is a graph showing the results of an *in vitro* regulatory T cell (Treg) suppression assay using CD3 stimulated primed-T cells (isolated from the LN of dry eye mice) and Tregs (isolated from the LN of mice treated with anti-IL-17 or isotype antibodies). The data show a significant recovery in the suppressor potential of Tregs only in mice treated with anti-IL-17 antibody (i.p.) compared to those isolated from the isotype antibody treated

groups ($p = 0.029$). The suppressor potential of Tregs isolated from different groups is calculated in relation to the suppression potential of Tregs of normal mice, considered as 100%. The data suggest a reversal of regulatory-T cell (Treg) suppressor function by anti-IL-17 therapy.

[68] Figure 8A is a schematic diagram of the experimental design to study the effects of *in vivo* IL-17 blockade using topical application of anti-IL-17 antibody or isotype-antibody on clinical signs.

[69] Figure 8B is a graph showing corneal fluorescein staining (CFS) scores, a readout for the principal clinical sign of dry eye, in anti-IL-17 antibody-treated, isotype antibody-treated and untreated groups from Day 4 (base line) to Day 10.

[70] Figure 8C is a graph showing the percent change in CFS scores at Day 10 from baseline CFS scores (Day 4) in different groups. CFS scores are significantly lower in anti-IL-17 antibody-treated mice compared to isotype antibody-treated and untreated groups.

[71] Figure 9 is a pair of graphs showing that topical application of anti-IL-17 antibody reduces frequencies of pathogenic Th17 cells both in conjunctiva (Conj) (left) and the draining lymph nodes (LN) (right). Conjunctiva and the draining lymph nodes were harvested at day 10 (as shown in Fig. 8) from anti-IL-17 antibody and isotype antibody treated mice. Real-time PCR was performed to analyze mRNA expression levels of IL-17 (Th17 cells) and Foxp3 (Treg cells). Dotted line represents mRNA levels in normal controls.

[72] Figure 10A is a series of micrographs showing that topical application of anti-IL-17 antibody inhibits dry eye induced corneal lymphatic vessels via decreased secretion of lymphangiogenesis-specific growth factors, particularly VEGF-C and -D in dry eye corneas. Induction of new lymphatic vessels in dry eye corneas facilitate the migration of resident corneal antigen presenting cells to the draining lymph nodes which in turn induce generation of adaptive immunity to ocular surface. Representative micrographs of corneal whole mounts showing lymphatic vessels (LV) and blood vessels (BV) in different groups.

[73] Figure 10B is a graph showing that topical application of anti-IL-17 antibody inhibits dry eye induced corneal lymphatic vessels via decreased secretion of lymphangiogenesis-specific growth factors, particularly VEGF-C and -D in dry eye corneas. Induction of new lymphatic vessels in dry eye corneas facilitate the migration of resident corneal antigen presenting cells to the draining lymph nodes which in turn induce generation of adaptive immunity to ocular surface. Real-time PCR analysis of whole cornea showing mRNA levels of Interleukin-1 (IL1)-beta, IL1-alpha, and lymphatic vessel-specific growth factors VEGF-C

and -D, and their cognate receptor, VEGFR-3. Dotted line represents mRNA levels in cornea of normal controls.

[74] Figure 11 is a series of micrographs and associated key showing that topical application of anti-IL-17 antibody maintains the normal phenotype of CD11b+ cells in cornea. Representative micrographs showing CD11b staining in corneas of different groups. Corneas of Anti-IL17-antibody treated group show that similar to normal cornea, majority of CD11b+ cells have phenotype of resident dendritic cells. However, corneas of Isotype-antibody treated group show that phenotype of majority of CD11b+ cells are similar to the infiltrating pathogenic macrophages/monocytes.

[75] Figure 12 is a series of micrographs showing that topical application of anti-IL-17 antibody prevents corneal nerve degeneration. Representative micrographs of corneal whole mount showing epithelial and sub-epithelial nerves (Tubulin-III, Red) in different groups. Patterns of nerves in the corneas of Anti-IL17-antibody treated group show similarity to those in the normal corneas, whereas corneas of Isotype-antibody treated group show loss of epithelial nerves.

[76] Figure 13 is a schematic representation of the vicious circle of epithelial disease to nerve damage. IL-17 mediates corneal epithelial cell and nerve damage. Nerve damage can in turn exacerbate epithelial disease by lower provision of trophic factors necessary for epithelial cell health. The resultant increased level of inflammation and IL-17 overexpression also leads to lymphatic vessel invasion or growth into the cornea and the activation of immune cells, allowing the immune cells easier access from the cornea to the lymphoid compartment where autoimmunity is generated and chronic diseases sustained.

[77] Figure 14A is a schematic diagram of the experiments performed to generate the data of Figure 14B.

[78] Figure 14B is a graph of the fold change in mRNA levels of lymphangiogenesis growth factors, such as VEGF-A, VEGF-C, and VEGF-D, in human corneal epithelial cells treated with human-r-IL-17 (5 ng/ml).

DETAILED DESCRIPTION

Ocular Surface Inflammatory Disorders:

[79] DES is a predominant ocular surface inflammatory disorder, however, other disorders are contemplated. Exemplary contemplated ocular surface inflammatory disorders include, but are not limited to, penetrating keratoplasty (corneal transplantation), corneal neovascularization, allergy, conjunctivitis, and microbial keratitis. Contemplated disorders

can be caused by autoimmune mechanisms, bone marrow transplant, surgery (general eye surgery, corneal transplantation, refractive surgery, LASIK), allergy, infection, trauma, injury, drug use, tear film abnormalities, contact lens use, neovascularization, tumor formation or growth, exposure to airborne or liquid irritants, hormonal variation, deprivation of essential fatty acids, and genetic predisposition.

Dry Eye Syndrome (DES):

[80] DES and related diseases can be caused by autoimmune and environmental conditions as well as any activity that decreases the rate of blinking. Alternatively, DES and related diseases are caused by decreased tear production or a change in tear composition that results in inadequate lubrication of the eye. Contact lens use, eye surgery, and eye injury can induce DES. Finally, DES often occurs as a consequence of aging and hormonal changes.

[81] Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (emp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes. *CLAO J* 1995;21:221-2). For a more detailed definition, see The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. Ocular Surface. 2007 Apr;5(2):75-92. The method of therapy inhibits or reduces the severity of at least one of these signs or symptoms.

[82] Synonyms and related diseases of DES include, but are not limited to, keratoconjunctivitis sicca (KCS), Sjögren syndrome (SS), Sjögren syndrome associated keratoconjunctivitis sicca, non-Sjögren syndrome associated keratoconjunctivitis sicca, keratitis sicca, sicca syndrome, xerophthalmia, tear film disorder, decreased tear production, aqueous tear deficiency (ATD), meibomian gland dysfunction, and evaporative loss. The subject is identified as suffering from DES or a related disorder by detecting a sign or symptom selected from the group consisting of dry, scratchy, stingy, itchy, burning or pressured sensations, irritation, pain, redness, inflammation, discharge, and excessive eye watering. Alternatively, a subject is identified as suffering from DES or a related disorder if their tear composition is insufficient for proper eye tissue lubrication. The method of therapy inhibits or reduces the severity of at least one of these signs or symptoms.

Th17 Cells

[83] T lymphocytes are circulating small white blood cells that play a central role in cell-mediated immunity. T helper cells (Th), also known as effector T cells, are one subgroup of T

lymphocytes. Th17 cells are a recently-identified population of T helper cells that produce Interleukin-17 (IL-17) and have been shown to contribute to autoimmune conditions. Importantly, these cells have not been previously implicated in DES.

Determination of IL-17-Mediated Ocular Surface Inflammation

[84] Exemplary tests used to determine the occurrence and severity of ocular surface inflammation include, but are not limited to, the following:

The Surface Disease Index (OSDI)

[85] The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire that provides a rapid assessment of the symptoms of ocular irritation consistent with ocular surface inflammatory disorders, including DES, and their impact on vision-related functioning (Figure 6). The 12 items of the OSDI questionnaire are graded on a scale of 0 to 4, where 0 indicates none of the time; 1, some of the time; 2, half of the time; 3, most of the time; and 4, all of the time. The total OSDI score is then calculated on the basis of the following formula: OSDI=[(sum of scores for all questions answered) x 100]/[(total number of questions answered) x 4]. Thus, the OSDI is scored on a scale of 0 to 100, with higher scores representing greater disability. A negative change from baseline indicates an improvement in vision-related function and the ocular inflammatory disorders described herein. For the therapeutic method described herein, treatment is considered more effective than control (vehicle) as indicated by a mean change (decrease) from baseline for the OSDI of >10 units compared to control.

[86] Therapeutic treatment is considered more effective than the vehicle as indicated by a mean change from baseline of average score (0 -100) for the Ocular Surface Disease Index (OSDI) of >10 units better than vehicle.

Corneal and Conjunctival Staining

[87] Corneal staining is a measure of epithelial disease, or break in the epithelial barrier of the ocular surface, typically seen with ocular surface inflammatory disorders such as DES, among others. Importantly, corneal staining can exist even without clinically evident dry eye, if there is significant lid disease, such as posterior blepharitis. Corneal staining is highly correlated with ocular discomfort in many, though not all patients; in general corneal staining is associated with high scores in the OSDI, as described above. For corneal fluorescein staining, saline-moistened fluorescein strips or 1% sodium fluorescein solution are used to stain the tear film. The entire cornea is then examined using slit-lamp evaluation with a yellow barrier filter (#12 Wratten) and cobalt blue illumination (staining is more intense

when it is observed with a yellow filter). Staining is graded according to the Oxford Schema (Figure 5).

[88] Conjunctival staining is a measure of epithelial disease or break in the epithelial barrier of the ocular surface, typically seen with ocular surface inflammatory disorders such as DES, among others. Importantly, conjunctival staining, similar to corneal staining, can exist even without clinically evident dry eye, if there is significant lid disease, such as posterior blepharitis. Conjunctival staining can also correlate with symptoms of ocular irritation and high OSDI scores as described above. Conjunctival staining is performed under the slit-lamp using lissamine green. Saline-moistened strip or 1% lissamine green solution is used to stain the tear film, and interpalpebral conjunctival staining is evaluated more than 30 seconds, but less than 2 minutes, later. Using white light of moderate intensity, only the interpalpebral region of the nasal and temporal conjunctival staining is graded using the Oxford Schema (Figure 5). The treatment described herein leads to decreases in ocular staining scores beyond what is observed with the vehicle alone.

[89] Therapeutic treatment is considered more effective than vehicle as indicated by a mean change from baseline in average score (0-5 scale) for corneal and conjunctival staining of > 1 unit better than vehicle, e.g. as detected using the Oxford Schema.

Schirmer Test

[90] The Schirmer test is performed in the presence and in the absence of anesthesia by placing a narrow filter-paper strip (5 x 3 5mm strip of Whatman™ #41 filter paper) in the inferior cul-de-sac. This test is conducted in a dimly lit room. The patient gently closes his/her eyes until five minutes have elapsed and the strips are removed. Because the tear front will continue advancing a few millimeters after it has been removed from the eyes, the tear front is marked with a ball-point pen at precisely five minutes. Aqueous tear production is measured by the length in millimeters that the strip wets during 5 minutes. Results of 10 mm or less for the Schirmer test without anesthesia and 5 mm or less for the Schirmer test with anesthesia are considered abnormal. A positive change from baseline indicates improvement of one or more symptoms of an ocular inflammatory disorder described herein.

Conjunctiva Hyperemia

[91] Bulbar conjunctival hyperemia is graded as follows:

None	(0):	none
Mild	(1):	slight localized injection
Moderate	(2):	pink color, confined to palpebral or bulbar conjunctiva
Severe	(3):	red color of the palpebral and/or bulbar conjunctiva
Very Severe	(4):	marked dark redness of the palpebral and/or bulbar conjunctiva

The presence or absence of tarsal papillary hypertrophy is also noted.

Impression Cytology

[92] Filter paper or other collection devices are used to collect cells and liquid samples from the ocular surface, tear ducts, or meibomian glands to be tested for the presence and/or abundance of an IL-17 cytokine, an IL-17 receptor, and/or a Th17 cell. The presence and/or abundance of RNA, DNA, or protein relating to an IL-17 cytokine or IL-17 receptor is determined by standard methods including, but not limited to, polymerase chain reaction (PCR), reverse transcriptase PCR (RT-PCR), gel electrophoresis, probe hybridization, antibody detection, in situ hybridization, Western blot, Northern Blot, Southern Blot, fluorescent microscopy, flow cytometry, enzyme-linked immunosorbant assay (ELISA), immunoprecipitation, gene chip analysis, protein chip analysis, cell culture methods, and cell sorting (see, Gulati A, Sacchetti M, Bonini S, Dana R. Chemokine Receptor CCR5 Expression in Conjunctival Epithelium of Patients with Dry Eye Syndrome. *Arch Ophthalmol* 2006; 124: 710-716; Argueso P, Balaram M, Spurr-Michaud S, Keutmann HT, Dana MR, Gipson IK. Decreased levels of goblet cell mucin MUC5AC in tears of Sjogren's syndrome patients. *Invest Ophthalmol Vis Sci.* 2002; 43: 1004-1011. Sambrook, J., Fritsch, E.F., and Maniatis, T., Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, NY, Vol. 1, 2, 3 (1989)).

Corneal Structure

[93] The cornea is the transparent front part of the eye that covers the iris, pupil, and anterior chamber. Together with the lens, the cornea refracts light, and as a result helps the eye to focus, accounting for approximately two-thirds of the eye's total optical power. The cornea has unmyelinated nerve endings sensitive to touch, temperature and chemicals; a touch of the cornea causes an involuntary reflex to close the eyelid. Because transparency is of prime importance the cornea does not have blood vessels; it receives nutrients via diffusion from the tear fluid at the outside and the aqueous humor at the inside and also from neurotrophins supplied by nerve fibers that innervate it. In humans, the cornea has a diameter of about 11.5 mm and a thickness of 0.5–0.6 mm in the center and 0.6–0.8 mm at the periphery.

[94] Transparency, avascularity, the presence of highly immature resident immune cells, and immunologic privilege makes the cornea a unique tissue. Immune privilege is meant to describe certain sites in the body that are able to tolerate the introduction of an antigen without eliciting an inflammatory immune response. The cornea has no blood supply, but rather, the cornea it gets oxygen directly through the air and the tears that bathe it. The human

cornea, like that of other primates, has five layers. From the anterior to posterior they are the corneal epithelium, Bowman's layer, the corneal stroma, Descemet's membrane, and the corneal endothelium. The corneal epithelium is a thin epithelial multicellular tissue layer, stratified squamous epithelium, of continuously regenerating cells, kept moist with tears. Irregularity or edema of the corneal epithelium disrupts the smoothness of the air-tear film interface, the most significant component of the total refractive power of the eye, thereby reducing visual acuity. Bowman's layer, also known as the anterior limiting membrane, is a condensed layer of irregularly-arranged collagen, about 8-14 microns thick, that protects the corneal stroma. The corneal stroma, also known as the substantia propria, is a thick and transparent middle layer, consisting of regularly-arranged collagen fibers along with sparsely populated keratocytes. The corneal stroma consists of approximately 200 layers of type I collagen fibrils. Ninety percent of the corneal thickness is composed of the stroma. Descemet's membrane, also known as the posterior limiting membrane, is a thin and acellular layer that serves as the modified basement membrane of the corneal endothelium. The corneal endothelium is a simple squamous or low cuboidal monolayer of mitochondria-rich cells responsible for regulating fluid and solute transport between the aqueous and corneal stromal compartments. The corneal endothelium is bathed by aqueous humor, not by blood or lymph, and has a very different origin, function, and appearance from vascular endothelia. Unlike the corneal epithelium, the cells of the endothelium do not regenerate. Instead, corneal endothelial cells expand or spread to compensate for dead cells which reduces the overall cell density of the endothelium and impacts fluid regulation.

[95] The cornea is one of the most sensitive tissues of the body, it is densely innervated with sensory nerve fibers via the ophthalmic division of the trigeminal nerve by way of 70 - 80 long and short ciliary nerves. Nerves enter the cornea via three levels, scleral, episcleral and conjunctival. Most of the bundles subdivide and form a network in the stroma, from which fibers supply different regions of the cornea. Three exemplary networks are midstromal, subepithelial/Bowman's layer, and epithelium. Corneal nerves of the subepithelial layer converge and terminate near the apex of the cornea.

Corneal Innervation

[96] The cornea is one of the most densely innervated tissues in the body and is abundantly supplied by different types of nerve fibers. Rabbit studies have revealed that the nerve density of the corneal epithelium is about 300-600 times as much as that of skin and 20-40 times that of the dental pulp. It is estimated that there are approximately 7000 sensory receptors per

mm^2 in the human corneal epithelium, implying that injuries to individual epithelial cells may be adequate to give a pain perception (Exp Eye Res 2003;76:521-42).

[97] Most corneal nerve fibers are sensory in origin and are derived from the ophthalmic branch of the trigeminal nerve. Nerve bundles enter the peripheral mid-stromal cornea in a radial fashion parallel to the corneal surface. Soon after entering the cornea, the main stromal bundles branch repeatedly and dichotomously into smaller fascicles that ascended into progressively more superficial layers of the stroma. Eventually the stromal nerve fibers turn abruptly 90°, penetrate Bowman's layer and proceed towards the corneal surface. After penetrating Bowman's layer, bundles divide and run parallel to the corneal surface between Bowman's layer and the basal epithelium, forming the subbasal nerve plexus. The density and number of nerves in the subbasal epithelial nerve plexus are significantly greater than the density and number of nerves in the remaining corneal layers. Subbasal fibers subsequently form branches that turn upward and enter the corneal epithelium between the basal cells to reach the wing cells, where they terminate (Invest Ophthalmol Vis Sci 1996;37:476-88).

[98] Corneal nerve fibers mediate not only sensation but also exert critical trophic influences on the corneal epithelium and play a vital role to the preservation of a healthy ocular surface. Corneal sensation is a key mechanism in preventing injury through the blink reflex and reflex tearing. Enhanced epithelial cell proliferation is mediated by neurotransmitters and nerve growth factors released from corneal nerve endings (Acta Ophthalmol Suppl 1989;192:115-34). Dysfunction of corneal innervation produces a degenerative condition known as neurotrophic keratitis, which therefore renders the corneal surface vulnerable to occult injury and delayed healing of established corneal epithelial injuries. Most clinical cases of neurotrophic keratitis are caused by herpes simplex or zoster keratitis, diabetes mellitus, or by trigeminal nerve damage associated with orbital or head surgery, head trauma, aneurysms, or intracranial neurologic disease. Absent or reduced corneal sensation may be congenital in origin. Keratorefractive procedures such as photorefractive keratectomy (PRK) and laser *in situ* keratomileusis (LASIK) can sever stromal and subbasal corneal nerves plexus and produce a transient mild to severe neurotrophic dry eye.

[99] Intact corneal innervation is also mandatory for tearing reflexes. Under normal physiological conditions, sensory nerves in the cornea transmit an afferent stimulation signal to the brain stem and then, after a series of interneurons, the efferent signal is transmitted to the lacrimal gland through the parasympathetic and sympathetic nerves that innervate the gland and drive tear production and secretion (Ocul Surf 2004;2:76-91). Damage to this

neural circuit interrupts the normal regulation of lacrimal gland secretion and causes dry eye disease. A reduction in neural drive from the cornea favors the occurrence of dry eye-associated ocular surface disease in two ways; first, by decreasing reflex-induced lacrimal secretion and by reducing the blink rate and, consequently, increasing evaporative loss; second, by decreasing the trophic factors to the epithelial layer. Damage to the sensory nerves in the ocular surface, particularly the cornea, as a consequence of refractive surgery and normal aging, prevents the normal reflex arc to the lacrimal gland and can result in decreased tear secretion and dry eye syndromes. Evidence for this mechanism comes from the clinical observation that dry eye syndrome frequently occurs after corneal refractive surgery. Clinical studies confirmed that tear production and secretion are reduced after LASIK surgery (Ophthalmology 2001;108:1230-5). Hyposecretion of tears in dry eye may lead to pathologic alterations in corneal nerves and a decline in corneal sensitivity which subsequently perpetuate the dry eye state (Cornea 1996;15:235-9).

Corneal Pathology

[100] Ocular diseases that affect the corneal epithelium such as dry eye, exposure keratopathy, and other ocular surface diseases cause corneal nerve degeneration. On the other hand, normal neural drive is an essential requirement for corneal epithelium to heal and maintain its homeostasis. Therefore, corneal nerve alterations, either as a primary reason (refractive surgery) or just as the outcome of dryness and other corneal epithelial or ocular surface diseases, have crucial effects on the homeostasis of corneal epithelium, thus neatly contributing to the increase of the vicious circle of epithelial disease and nerve damage.

The Relationship between Corneal Epithelial Disease and Corneal Nerve Damage

[101] Ocular diseases that affect the corneal epithelium such as dry eye, exposure keratopathy, and other ocular surface diseases cause corneal nerve degeneration. On the other hand, normal neural drive and function are essential requirements for corneal epithelial healing and the maintenance of corneal homeostasis. Therefore, corneal nerve damage, either as a primary reason (inflicted by refractory surgery, herpetic eye disease, diabetes, or trigeminal nerve damage, e.g. fifth cranial nerve damage) or as a secondary outcome of dryness and other corneal epithelial or ocular surface diseases, can cause further damage to the corneal epithelium, thus contributing to the increase of the vicious circle of epithelial disease and nerve damage. In addition, IL-1 and corneal epithelial disease induce lymphatic vessel formation in the cornea. These lymphatic vessels are crucial for migration of resident and infiltrating antigen presenting cells and other immune cells, and drainage of corneal antigens, to the lymphoid compartment including draining lymph nodes and induction of

adaptive immunity at the ocular surface, which ultimately leads to persistent and chronic ocular surface disease (see Figure 13).

The Relationship between Corneal Lymphatics and Inflammation

[102] The normal human cornea has no lymphatic vessels. However in pathological conditions such as corneal epithelial disease, IL-17 induces lymphatic vessel formation in the cornea. These lymphatic vessels are crucial for migration of resident and infiltrating antigen presenting cells and other immune cells, and drainage of corneal antigens, to the lymphoid compartment including draining lymph nodes and induction of adaptive immunity against ocular surface, which ultimately leads to persistent and chronic ocular surface disease (see Figure 13). In addition, corneal lymphatics play an important role in the induction of alloimmune response to corneal grafts in transplantations. The existence of corneal lymphatic vessels leads to increased rate of transplant rejections. Therapeutic inhibition of corneal lymphatics may thus enhance corneal transplant survival both in the high- and low-risk recipients.

Interleukin-17 (IL-17):

[103] Interleukin-17 (IL-17) is a potent proinflammatory cytokine produced by a new lineage of $CD4^+$ T cells (Th17). IL-17 signals through a heteromeric receptor complex composed of IL-17RA and IL-17RC. IL-17 has pleiotropic effects on several immune and non-immune cells, providing an association between T cell activation and the inflammatory response. Furthermore, IL-17 cooperates either additively or synergistically with other proinflammatory cytokines such as TNFα, IL1β or IL6, leading to amplification of inflammatory processes. IL-17, also known as IL-17A, is part of a larger family comprising 6 cytokines, referred to as IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. All members of this family share a common protein structure. Among these family members, IL-17A and IL-17F are most frequently expressed in immune cells. In alternative embodiments of the invention, one or more of these family members are targeted by antagonists to inhibit or modify their activity.

[104] The invention comprises compositions with means to inhibit or modify the activity of human IL-17, defined as the ability of this protein to bind an IL-17 receptor. Compositions that comprise an inhibitor of human IL-17 function antagonize the activity of an IL-17 receptor. The composition comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule, or a fragment thereof, with means to inhibit or modify the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding human IL-17. In a preferred embodiment, the

inhibitory composition binds to one or more region(s)/fragment(s) of IL-17 comprised by SEQ ID NO: 1 and SEQ ID NO: 2.

[105] A fragment, in the case of these sequences and all others provided herein, is defined as a part of the whole that is less than the whole. Moreover, a fragment ranges in size from a single nucleotide or amino acid within a polynucleotide or polypeptide sequence to one fewer nucleotide or amino acid than the entire polynucleotide or polypeptide sequence. Finally, a fragment is defined as any portion of a complete polynucleotide or polypeptide sequence, which is intermediate between the extremes defined above.

[106] Human IL-17 is encoded by the following mRNA sequence (NCBI Accession No. NM_002190, alternatively called IL-17A, and SEQ ID NO: 1): (For all mRNA transcripts incorporated into the present application, the initiator methionine, encoded by the codon "atg," is bolded and capitalized to delineate the start of the coding region.)

```
   1 gcaggcacaa actcatccat ccccagttga ttggaagaaa caacgATGac tcctgggaag
  61 acctcattgg tgtcactgct actgctgctg agcctggagg ccatagtgaa ggcaggaatc
 121 acaatcccac gaaatccagg atgcccaaat tctgaggaca agaacttccc ccggactgtg
 181 atggtcaacc tgaacatcca taaccggaat accaatacca atcccaaaag gtcctcagat
 241 tactacaacc gatccacctc accttggaat ctccaccgca atgaggaccc tgagagatat
 301 ccctctgtga tctgggaggc aaagtgccgc cacttgggct gcatcaacgc tgatgggaac
 361 gtggactacc acatgaactc tgtccccatc cagcaagaga tcctggtcct gcgcagggag
 421 cctccacact gccccaactc cttccggctg gagaagatac tggtgtccgt gggctgcacc
 481 tgtgtcaccc cgattgtcca ccatgtggcc taagagctct ggggagccca cactccccaa
 541 agcagttaga ctatggagag ccgacccagc ccctcaggaa ccctcatcct tcaaagacag
 601 cctcatttcg gactaaactc attagagttc ttaaggcagt ttgtccaatt aaagcttcag
 661 aggtaacact tggccaagat atgagatctg aattaccttt ccctctttcc aagaaggaag
 721 gtttgactga gtaccaattt gcttcttgtt tacttttta agggctttaa gttatttatg
 781 tatttaatat gccctgagat aactttgggg tataagattc cattttaatg aattacctac
 841 tttattttgt ttgtcttttt aaagaagata agattctggg cttgggaatt ttattattta
 901 aaaggtaaaa cctgtattta tttgagctat ttaaggatct atttatgttt aagtatttag
 961 aaaaaggtga aaaagcacta ttatcagttc tgcctaggta aatgtaagat agaattaaat
1021 ggcagtgcaa aatttctgag tctttacaac atacggatat agtatttcct cctctttgtt
1081 tttaaaagtt ataacatggc tgaaaagaaa gattaaacct actttcatat gtattaattt
1141 aaattttgca atttgttgag gttttacaag agatacagca agtctaactc tctgttccat
1201 taaaccctta taataaaatc cttctgtaat aataaagttt caaaagaaaa tgtttatttg
1261 ttctcattaa atgtatttta gcaaactcag ctcttcccta ttgggaagag ttatgcaaat
1321 tctcctataa gcaaaacaaa gcatgtcttt gagtaacaat gacctggaaa tacccaaaat
1381 tccaagttct cgatttcaca tgccttcaag actgaacacc gactaaggtt ttcatactat
1441 tagccaatgc tgtagacaga agcattttga taggaataga gcaaataaga taatggccct
1501 gaggaatggc atgtcattat taaagatcat atggggaaaa tgaaaccctc cccaaaatac
1561 aagaagttct gggaggagac attgtcttca gactacaatg tccagtttct cccctagact
1621 caggcttcct ttggagatta aggcccctca gagatcaaca gaccaacatt tttctcttcc
1681 tcaagcaaca ctcctagggc ctggcttctg tctgatcaag gcaccacaca acccagaaag
1741 gagctgatgg ggcagaacga actttaagta tgagaaaagt tcagcccaag taaaataaaa
1801 actcaatcac attcaattcc agagtagttt caagtttcac atcgtaacca ttttcgccc
```

[107] Human IL-17 is encoded by the following amino acid sequence (NCBI Accession No. NM_002190, alternatively called IL-17A, and SEQ ID NO: 2):

MTPGKTSLVSLLLLLSLEAIVKAGITIPRNPGCPNSEDKNFPRTVMVNLNIHNRNTNTNPKRSSDYYNRS
TSPWNLHRNEDPERYPSVIWEAKCRHLGCINADGNVDYHMNSVPIQQEILVLRREPPHCPNSFRLEKIL
VSVGCTCVTPIVHHVA.

[108] Human IL-17B is encoded by the following mRNA sequence (NCBI Accession No. NM_014443 and SEQ ID NO: 3):

```
  1 tggggttcca ggcgggcagc agctgcaggc tgaccttgca gcttggcgga ATGgactggc
 61 ctcacaacct gctgtttctt cttaccattt ccatcttcct ggggctgggc cagcccagga
121 gccccaaaag caagaggaag gggcaagggc ggcctgggcc cctggccccc ggccctcacc
181 aggtgccact ggacctggtg tcacggatga aaccgtatgc ccgcatggag gagtatgaga
241 ggaacatcga ggagatggtg gcccagctga ggaacagctc agagctggcc cagagaaagt
301 gtgaggtcaa cttgcagctg tggatgtcca acaagaggag cctgtctccc tggggctaca
361 gcatcaacca cgaccccagc cgtatccccg tggacctgcc ggaggcacgg tgcctgtgtc
421 tgggctgtgt gaacccctcc accatgcagg aggaccgcag catggtgagc gtgccggtgt
481 tcagccaggt tcctgtgcgc cgccgcctct gcccgccacc gccccgcaca gggccttgcc
541 gccagcgcgc agtcatggag accatcgctg tgggctgcac ctgcatcttc tgaatcacct
601 ggcccagaag ccaggccagc agcccgagac catcctcctt gcacctttgt gccaagaaag
661 gcctatgaaa agtaaacact gacttttgaa agcaaaaaaa aaaaaaaaaa a
```

[109] Human IL-17B is encoded by the following amino acid sequence (NCBI Accession No. NM_014443 and SEQ ID NO: 4):

MDWPHNLLFLLTISIFLGLGQPRSPKSKRKGQGRPGPLAPGPHQVPLDLVSRMKPYARMEEYERNIEEM
VAQLRNSSELAQRKCEVNLQLWMSNKRSLSPWGYSINHDPSRIPVDLPEARCLCLGCVNPFTMQEDRS
MVSVPVFSQVPVRRRLCPPPPRTGPCRQRAVMETIAVGCTCIF

[110] Human IL-17C is encoded by the following mRNA sequence (NCBI Accession No. NM_013278 and SEQ ID NO: 5):

```
   1 gccaggtgtg caggccgctc caagcccagc ctgccccgct gccgccacca tgacgctcct
  61 ccccggcctc ctgtttctga cctggctgca cacatgcctg gcccaccatg acccctccct
 121 caggggggcac ccccacagtc acggtacccc acactgctac tcggctgagg aactgccccct
 181 cggccaggcc cccccacacc tgctggctcg aggtgccaag tgggggcagg ctttgcctgt
 241 agccctggtg tccagcctgg aggcagcaag ccacaggggg aggcacgaga ggccctcagc
 301 tacgacccag tgcccggtgc tgcggccgga ggaggtgttg gaggcagaca cccaccagcg
 361 ctccatctca ccctggagat accgtgtgga cacggatgag gaccgctatc cacagaagct
 421 ggccttcgcc gagtgcctgt gcagaggctg tatcgatgca cggacgggcc gcgagacagc
 481 tgcgctcaac tccgtgcggc tgctccagag cctgctggtg ctgcgccgcc ggccctgctc
 541 ccgcgacggc tcggggctcc ccacacctgg ggcctttgcc ttccacaccg agttcatcca
 601 cgtccccgtc ggctgcacct gcgtgctgcc ccgttcagtg tgaccgccga ggccgtgggg
 661 cccctagact ggacacgtgt gctccccaga gggcaccccc tatttatgtg tatttattgt
 721 tatttatatg cctcccccaa cactaccctt ggggtctggg cattccccgt gtctggagga
 781 cagccccca ctgttctcct catctccagc ctcagtagtt gggggtagaa ggagctcagc
 841 acctcttcca gcccttaaag ctgcagaaaa ggtgtcacac ggctgcctgt accttggctc
 901 cctgtcctgc tcccggcttc ccttacccta tcactggcct caggcccccg caggctgcct
 961 cttcccaacc tccttggaag tacccctgtt tcttaaacaa ttatttaagt gtacgtgtat
1021 tattaaactg atgaacacat ccccaaaa
```

[111] Human IL-17C is encoded by the following amino acid sequence (NCBI Accession No. NM_013278 and SEQ ID NO: 6):

MTLLPGLLFLTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPHLLARGAKWGQALPVALVS
SLEAASHRGRHERPSATTQCPVLRPEEVLEADTHQRSISPWRYRVDTDEDRYPQKLAFAECLCRGCIDA
RTGRETAALNSVRLLQSLLVLRRRPCSRDGSGLPTPGAFAFHTEFIHVPVGCTCVLPRSV

[112] Human IL-17D is encoded by the following mRNA sequence (NCBI Accession No. NM_138284 and SEQ ID NO: 7):

```
   1 aaaatgtttt cagctcctgg aggcgaaagg tgcagagtcg ctctgtgtcc gtgaggccgg
  61 gcggcgacct cgctcagtcg gcttctcggt ccgagtcccc gggtctggAT Gctggtagcc
```

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 121 ggcttcctgc tggcgctgcc gccgagctgg gccgcgggcg ccccgagggc gggcaggcgc
 181 cccgcgcggc cgcggggctg cgcggaccgg ccggaggagc tactggagca gctgtacggg
 241 cgcctggcgg ccggcgtgct cagtgccttc caccacacgc tgcagctggg gccgcgtgag
 301 caggcgcgca acgcgagctg cccggcaggg ggcaggcccg ccgaccgccg cttccggccg
 361 cccaccaacc tgcgcagcgt gtcgccctgg gcctacagaa tctcctacga cccggcgagg
 421 taccccaggt acctgcctga agcctactgc ctgtgccggg gctgcctgac cgggctgttc
 481 ggcgaggagg acgtgcgctt ccgcagcgcc cctgtctaca tgcccaccgt cgtcctgcgc
 541 cgcacccccg cctgcgccgg cggccgttcc gtctacaccg aggcctacgt caccatcccc
 601 gtgggctgca cctgcgtccc cgagccggag aaggacgcag acagcatcaa ctccagcatc
 661 gacaaacagg gcgccaagct cctgctgggc cccaacgacg cgcccgctgg cccctgaggc
 721 cggtcctgcc ccgggaggtc tccccggccc gcatcccgag gcgcccaagc tggagccgcc
 781 tggagggctc ggtcggcgac ctctgaagag agtgcaccga gcaaaccaag tgccggagca
 841 ccagcgccgc ctttccatgg agactcgtaa gcagcttcat ctgacacggg catccctggc
 901 ttgcttttag ctacaagcaa gcagcgtggc tggaagctga tgggaaacga cccggcacgg
 961 gcatcctgtg tgcggcccgc atggagggtt tggaaaagtt cacggaggct ccctgaggag
1021 cctctcagat cggctgctgc gggtgcaggg cgtgactcac cgctgggtgc ttgccaaaga
1081 gatagggacg catatgcttt ttaaagcaat ctaaaaataa taataagtat agcgactata
1141 tacctacttt taaaatcaac tgttttgaat agaggcagag ctattttata ttatcaaatg
1201 agagctactc tgttacattt cttaacatat aaacatcgtt ttttacttct tctggtagaa
1261 ttttttaaag cataattgga atccttggat aaattttgta gctggtacac tctggcctgg
1321 gtctctgaat tcagcctgtc accgatggct gactgatgaa atggacacgt ctcatctgac
1381 ccactcttcc ttccactgaa ggtcttcacg ggcctccagg tggaccaaag ggatgcacag
1441 gcggctcgca tgccccaggg ccagctaaga gttccaaaga tctcagattt ggttttagtc
1501 atgaatacat aaacagtctc aaactcgcac aatttttttcc ccctttgaa agccactggg
1561 gccaatttgt ggttaagagg tggtgagata agaagtggaa cgtgacatct ttgccagttg
1621 tcagaagaat ccaagcaggt attggcttag ttgtaagggc tttaggatca ggctgaatat
1681 gaggacaaag tgggccacgt tagcatctgc agagatcaat ctggaggctt ctgtttctgc
1741 attctgccac gagagctagg tccttgatct tttctttaga ttgaaagtct gtctctgaac
1801 acaattattt gtaaaagtta gtagttcttt tttaaatcat taaaagaggc ttgctgaagg
1861 aaaaaaaaaa aaa
```

[113] Human IL-17D is encoded by the following amino acid sequence (NCBI Accession No. NM_138284 and SEQ ID NO: 8)

MLVAGFLLALPPSWAAGAPRAGRRPARPRGCADRPEELLEQLYGRLAAGVLSAFHHTLQLGPREQAR
NASCPAGGRPADRRFRPPTNLRSVSPWAYRISYDPARYPRYLPEAYCLCRGCLTGLFGEEDVRFRSAPV
YMPTVVLRRTPACAGGRSVYTEAYVTIPVGCTCVPEPEKDADSINSSIDKQGAKLLLGPNDAPAGP

[114] Human IL-17E is encoded by the following mRNA sequence (NCBI Accession No. AF305200 and SEQ ID NO: 9):

```
   1 ggcttgctga aaataaaatc aggactccta acctgctcca gtcagcctgc ttccacgagg
  61 cctgtcagtc agtgcccgac ttgtgactga gtgtgcagtg cccagcatgt accaggtcag
 121 tgcagagggc tgcctgaggg ctgtgctgag agggagagga gcagagatgc tgctgagggt
 181 ggagggaggc caagctgcca ggtttggggc tgggggccaa gtggagtgag aaactgggat
 241 cccaggggga gggtgcagat gagggagcga cccagattag gtgaggacag ttctctcatt
 301 agccttttcc tacaggtggt tgcattcttg gcaatggtca tgggaaccca cacctacagc
 361 cactggccca gctgctgccc cagcaaaggg caggacacct ctgaggagct gctgaggtgg
 421 agcactgtgc ctgtgcctcc cctagagcct gctaggccca accgccaccc agagtcctgt
 481 agggccagtg aagatggacc cctcaacagc agggccatct ccccctggag atatgagttg
 541 gacagagact tgaaccggct cccccaggac ctgtaccacg cccgttgcct gtgcccgcac
 601 tgcgtcagcc tacagacagg ctcccacatg gacccccggg gcaactcgga gctgctctac
 661 cacaaccaga ctgtcttcta caggcggcca tgccatggcg agaagggcac ccacaagggc
 721 tactgcctgg agcgcaggct gtaccgtgtt tccttagctt gtgtgtgtgt gcggccccgt
 781 gtgatgggct agccggacct gctggaggct ggtccctttt tgggaaacct ggagccaggt
 841 gtacaaccac ttgccatgaa gggccaggat gcccagatgc ttggcccctg tgaagtgctg
 901 tctggagcag caggatcccg ggacaggatg gggggctttg gggaaaacct gcacttctgc
 961 acattttgaa aagagcagct gctgcttagg gccgccggaa gctggtgtcc tgtcattttc
1021 tctcaggaaa ggttttcaaa gttctgccca tttctggagg ccaccactcc tgtctcttcc
1081 tcttttccca tcccctgcta ccctggccca gcacaggcac tttctagata tttccccctt
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1141 gctggagaag aaagagcccc tggttttatt tgtttgttta ctcatcactc agtgagcatc
1201 tactttgggt gcattctagt gtagttacta gtcttttgac atggatgatt ctgaggagga
1261 agctgttatt gaatgtatag agatttatcc aaataaatat ctttatttaa aaatgaaaaa
1321 aaaaaaaaaa aaaaa
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[115] Human IL-17E is encoded by the following amino acid sequence (NCBI Accession No. AF305200 and SEQ ID NO: 10):

MRERPRLGEDSSLISLFLQVVAFLAMVMGTHTYSHWPSCCPSKGQDTSEELLRWSTVPVPPLEPARPNR
HPESCRASEDGPLNSRAISPWRYELDRDLNRLPQDLYHARCLCPHCVSLQTGSHMDPRGNSELLYHNQ
TVFYRRPCHGEKGTHKGYCLERRLYRVSLACVCVRPRVMG

[116] Human IL-17F is encoded by the following mRNA sequence (NCBI Accession No. NM_052872 and SEQ ID NO: 11):

```
  1 gaacacaggc atacacagga agatacattc acagaaagag cttcctgcac aaagtaagcc
 61 accagcgcaa cATGacagtg aagaccctgc atggcccagc catggtcaag tacttgctgc
121 tgtcgatatt ggggcttgcc tttctgagtg aggcggcagc tcggaaaatc cccaaagtag
181 gacatacttt tttccaaaag cctgagagtt gcccgcctgt gccaggaggt agtatgaagc
241 ttgacattgg catcatcaat gaaaaccagc gcgtttccat gtcacgtaac atcgagagcc
301 gctccacctc cccctggaat tacactgtca cttgggaccc caaccggtac ccctcggaag
361 ttgtacaggc ccagtgtagg aacttgggct gcatcaatgc tcaaggaaag gaagacatct
421 ccatgaattc cgttcccatc cagcaagaga ccctggtcgt ccggaggaag caccaaggct
481 gctctgtttc tttccagttg gagaaggtgc tggtgactgt tggctgcacc tgcgtcaccc
541 ctgtcatcca ccatgtgcag taagaggtgc atatccactc agctgaagaa gctgtagaaa
601 tgccactcct tacccagtgc tctgcaacaa gtcctgtctg acccccaatt ccctccactt
661 cacaggactc ttaataagac ctgcacggat ggaaacagaa aatattcaca atgtatgtgt
721 gtatgtacta cactttatat ttgatatcta aaatgttagg agaaaaatta atatattcag
781 tgctaatata ataaagtatt aataattt
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[117] Human IL-17F is encoded by the following amino acid sequence (NCBI Accession No. NM_052872 and SEQ ID NO: 12)

MTVKTLHGPAMVKYLLLSILGLAFLSEAAARKIPKVGHTFFQKPESCPPVPGGSMKLDIGIINENQRVS
MSRNIESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNSVPIQQETLVVRRKHQGC
SVSFQLEKVLVTVGCTCVTPVIHHVQ

Interleukin-17 Receptors:

[118] The composition of the invention comprises a polynucleotide, a polypeptide, an antibody, a compound, or a small molecule, or fragment thereof, with means to inhibit or modify the transcription, transcript stability, translation, modification, localization, secretion, or function of a polynucleotide or polypeptide encoding an IL-17 receptor. One contemplated IL-17 heteromeric receptor complex comprises IL-17RA and IL-17RC. The present composition comprises a compound that is targeted to either element, IL-17RA or IL-17RC, of this receptor complex. IL-17RC exists in three different forms comprised by transcripts 1-3. However, additional IL-17 receptors are contemplated. In alternative embodiments, IL-17RB, IL-17RD, and IL-17RE are targeted in isolation or in combination by antagonists of IL-17 function. The invention comprises one or more antagonists of IL-17 receptors IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE.

[119] IL-17RA is encoded by the following mRNA sequence (NCBI Accession No. NM_014339 and SEQ ID NO: 13):

```
   1 ctgggcccgg gctggaagcc ggaagcgagc aaagtggagc cgactcgaac tccaccgcgg
  61 aaaagaaagc ctcagaacgt tcgttcgctg cgtccccagc cggggccgag ccctccgcga
 121 cgccagccgg gccATGgggg ccgcacgcag cccgccgtcc gctgtcccgg ggcccctgct
 181 ggggctgctc ctgctgctcc tgggcgtgct ggccccgggt ggcgcctccc tgcgactcct
 241 ggaccaccgg gcgctggtct gctcccagcc ggggctaaac tgcacggtca agaatagtac
 301 ctgcctggat gacagctgga ttcaccctcg aaacctgacc ccctcctccc caaaggacct
 361 gcagatccag ctgcactttg cccacaccca acaaggagac ctgttccccg tggctcacat
 421 cgaatggaca ctgcagacag acgccagcat cctgtacctc gagggtgcag agttatctgt
 481 cctgcagctg aacaccaatg aacgtttgtg cgtcaggttt gagtttctgt ccaaactgag
 541 gcatcaccac aggcggtggc gttttacctt cagccacttt gtggttgacc ctgaccagga
 601 atatgaggtg accgttcacc acctgcccaa gcccatccct gatggggacc caaaccacca
 661 gtccaagaat ttccttgtgc ctgactgtga gcacgccagg atgaaggtaa ccacgccatg
 721 catgagctca ggcagcctgt gggaccccaa catcaccgtg gagaccctgg aggcccacca
 781 gctgcgtgtg agcttcaccc tgtggaacga atctacccat taccagatcc tgctgaccag
 841 ttttccgcac atggagaacc acagttgctt tgagcacatg caccacatac ctgcgcccag
 901 accagaagag ttccaccagc gatccaacgt cacactcact ctacgcaacc ttaaagggtg
 961 ctgtcgccac caagtgcaga tccagccctt cttcagcagc tgcctcaatg actgcctcag
1021 acactccgcg actgtttcct gcccagaaat gccagacact ccagaaccaa ttccggacta
1081 catgcccctg tgggtgtact ggttcatcac gggcatctcc atcctgctgg tgggctccgt
1141 catcctgctc atcgtctgca tgacctggag gctagctggg cctggaagtg aaaaatacag
1201 tgatgacacc aaatacaccg atggcctgcc tgcggctgac ctgatccccc caccgctgaa
1261 gcccaggaag gtctggatca tctactcagc cgaccacccc ctctacgtgg acgtggtcct
1321 gaaattcgcc cagttcctgc tcaccgcctg cggcacggaa gtggccctgg acctgctgga
1381 agagcaggcc atctcggagg caggagtcat gacctgggtg ggccgtcaga agcaggagat
1441 ggtggagagc aactctaaga tcatcgtcct gtgctcccgc ggcacgcgcg ccaagtggca
1501 ggcgctcctg ggccgggggg cgcctgtgcg gctgcgctgc gaccacggaa agcccgtggg
1561 ggacctgttc actgcagcca tgaacatgat cctcccggac ttcaagaggc cagcctgctt
1621 cggcacctac gtagtctgct acttcagcga ggtcagctgt gacggcgacg tccccgacct
1681 gttcggcgcg gcgccgcggt acccgctcat ggacaggttc gaggaggtgt acttccgcat
1741 ccaggacctg gagatgttcc agccgggccg catgcaccgc gtaggggagc tgtcgggggа
1801 caactacctg cggagcccgg gcggcaggca gctccgcgcc gccctggaca ggttccggga
1861 ctggcaggtc cgctgtcccg actggttcga atgtgagaac ctctactcag cagatgacca
1921 ggatgccccg tccctggacg aagaggtgtt tgaggagcca ctgctgcctc cgggaaccgg
1981 catcgtgaag cgggcgcccc tggtgcgcga gcctggctcc caggcctgcc tggccataga
2041 cccgctggtc ggggaggaag gaggagcagc agtggcaaag ctggaacctc acctgcagcc
2101 ccggggtcag ccagcgccgc agcccctcca caccctggtg ctcgccgcag aggagggggc
2161 cctggtggcc gcggtggagc ctgggccccт ggctgacggt gccgcagtcc ggctggcact
2221 ggcgggggag ggcgaggcct gcccgctgct gggcagcccg ggcgctgggc gaaatagcgt
2281 cctcttcctc cccgtggacc ccgaggactc gcccccttggc agcagcaccc ccatggcgtc
2341 tcctgacctc cttccagagg acgtgaggga gcacctcgaa ggcttgatgc tctcgctctt
2401 cgagcagagt ctgagctgcc aggcccaggg gggctgcagt agacccgcca tggtcctcac
2461 agacccacac acgccctacg aggaggagca gcggcagtca gtgcagtctg accagggcta
2521 catctccagg agctccccgc agcccccga gggactcacg gaaatggagg aagaggagga
2581 agaggagcag gacccaggga agccggccct gccactctct cccgaggacc tggagagcct
2641 gaggagcctc cagcggcagc tgcttttccg ccagctgcag aagaactcgg gctgggacac
2701 gatggggtca gagtcagagg ggcccagtgc atgagggcgg ctccccaggg accgcccaga
2761 tcccagcttt gagagaggag tgtgtgtgca cgtattcatc tgtgtgtaca tgtctgcatg
2821 tgtatatgtt cgtgtgtgaa atgtaggctt taaaatgtaa atgtctggat tttaatccca
2881 ggcatccctc ctaacttttc tttgtgcagc ggtctggtta tcgtctatcc ccaggggaat
2941 ccacacagcc cgctcccagg agctaatggt agagcgtcct tgaggctcca ttattcgttc
3001 attcagcatt tattgtgcac ctactatgtg gcgggcattt gggataccaa gataaattgc
3061 atgcggcatg gccccagcca tgaaggaact taaccgctag tgccgaggac acgttaaacg
3121 aacaggatgg gccgggcacg gtggctcacg cctgtaatcc cagcacactg ggaggccgag
3181 gcaggtggat cactctgagg tcaggagttt gagccagcct ggccaacatg gtgaaacccc
3241 atctccacta aaaatagaaa aattagccgg gcatggtgac acatgcctgt agtcctagct
3301 acttgggagg ctgaggcagg agaattgctt gaatctggga ggcagaggtt gcagtgagcc
3361 gagattgtgc cattgcactg cagcctggat gacagagcga gactctatct caaaaaaaaa
3421 aaaaaaaaa
```

[120] IL-17RA is encoded by the following amino acid sequence (NCBI Accession No. NM_14339 and SEQ ID NO: 14):

MGAARSPPSAVPGPLLGLLLLLLGVLAPGGASLRLLDHRALVCSQPGLNCTVKNSTCLDDSWIHPRNL
TPSSPKDLQIQLHFAHTQQGDLFPVAHIEWTLQTDASILYLEGAELSVLQLNTNERLCVRFEFLSKLRHH
HRRWRFTFSHFVVDPDQEYEVTVHHLPKPIPDGDPNHQSKNFLVPDCEHARMKVTTPCMSSGSLWDP
NITVETLEAHQLRVSFTLWNESTHYQILLTSFPHMENHSCFEHMHHIPAPRPEEFHQRSNVTLTLRNLKG
CCRHQVQIQPFFSSCLNDCLRHSATVSCPEMPDTPEPIPDYMPLWVYWFITGISILLVGSVILLIVCMTWR
LAGPGSEKYSDDTKYTDGLPAADLIPPPLKPRKVWIIYSADHPLYVDVVLKFAQFLLTACGTEVALDLL
EEQAISEAGVMTWVGRQKQEMVESNSKIIVLCSRGTRAKWQALLGRGAPVRLRCDHGKPVGDLFTAA
MNMILPDFKRPACFGTYVVCYFSEVSCDGDVPDLFGAAPRYPLMDRFEEVYFRIQDLEMFQPGRMHR
VGELSGDNYLRSPGGRQLRAALDRFRDWQVRCPDWFECENLYSADDQDAPSLDEEVFEEPLLPPGTGI
VKRAPLVREPGSQACLAIDPLVGEEGGAAVAKLEPHLQPRGQPAPQPLHTLVLAAEEGALVAAVEPGP
LADGAAVRLALAGEGEACPLLGSPGAGRNSVLFLPVDPEDSPLGSSTPMASPDLLPEDVREHLEGLMLS
LFEQSLSCQAQGGCSRPAMVLTDPHTPYEEEQRQSVQSDQGYISRSSPQPPEGLTEMEEEEEEEQDPGK
PALPLSPEDLESLRSLQRQLLFRQLQKNSGWDTMGSESEGPSA

[121] IL-17RB is encoded by the following mRNA sequence (NCBI Accession No. NM_018725 and SEQ ID NO: 15):

```
   1 agcgtgcggg tggcctggat cccgcgcagt ggcccggcgA TGtcgctcgt gctgctaagc
  61 ctggccgcgc tgtgcaggag cgccgtaccc cgagagccga ccgttcaatg tggctctgaa
 121 actgggccat ctccagagtg gatgctacaa catgatctaa tccccggaga cttgagggac
 181 ctccgagtag aacctgttac aactagtgtt gcaacagggg actattcaat tttgatgaat
 241 gtaagctggg tactccgggc agatgccagc atccgcttgt tgaaggccac caagatttgt
 301 gtgacgggca aaagcaactt ccagtcctac agctgtgtga ggtgcaatta cacagaggcc
 361 ttccagactc agaccagacc ctctggtggt aaatggacat tttcctacat cggcttccct
 421 gtagagctga acacagtcta tttcattggg gcccataata ttcctaatgc aaatatgaat
 481 gaagatggcc cttccatgtc tgtgaatttc acctcaccag gctgcctaga ccacataatg
 541 aaatataaaa aaaagtgtgt caaggccgga agcctgtggg atccgaacat cactgcttgt
 601 aagaagaatg aggagacagt agaagtgaac ttcacaacca ctcccctggg aaacagatac
 661 atggctctta tccaacacag cactatcatc gggttttctc aggtgtttga gccacaccag
 721 aagaaacaaa cgcgagcttc agtggtgatt ccagtgactg gggatagtga aggtgctacg
 781 gtgcagctga ctccatattt tcctacttgt ggcagcgact gcatccgaca taaaggaaca
 841 gttgtgctct gcccacaaac aggcgtccct ttccctctgg ataacaacaa aagcaagccg
 901 ggaggctggc tgcctctcct cctgctgtct ctgctggtgg ccacatgggt gctggtggca
 961 gggatctatc taatgtggag gcacgaaagg atcaagaaga cttccttttc taccaccaca
1021 ctactgcccc ccattaaggt tcttgtggtt tacccatctg aaatatgttt ccatcacaca
1081 atttgttact tcactgaatt tcttcaaaac cattgcagaa gtgaggtcat ccttgaaaag
1141 tggcagaaaa agaaaatagc agagatgggt ccagtgcagt ggcttgccac tcaaaagaag
1201 gcagcagaca aagtcgtctt ccttctttcc aatgacgtca acagtgtgtg cgatggtacc
1261 tgtggcaaga gcgagggcag tcccagtgag aactctcaag acctcttccc ccttgccttt
1321 aacctttttct gcagtgatct aagaagccag attcatctgc acaaatacgt ggtggtctac
1381 tttagagaga ttgatacaaa agacgattac aatgctctca gtgtctgccc caagtaccac
1441 ctcatgaagg atgccactgc tttctgtgca gaacttctcc atgtcaagca gcaggtgtca
1501 gcaggaaaaa gatcacaagc ctgccacgat ggctgctgct ccttgtagcc cacccatgag
1561 aagcaagaga ccttaaaggc ttcctatccc accaattaca gggaaaaaac gtgtgatgat
1621 cctgaagctt actatgcagc ctacaaacag ccttagtaat taaaacattt tataccaata
1681 aaattttcaa atattgctaa ctaatgtagc attaactaac gattggaaac tacatttaca
1741 acttcaaagc tgttttatac atagaaatca attacagttt taattgaaaa ctataaccat
1801 tttgataatg caacaataaa gcatcttcag ccaaacatct agtcttccat agaccatgca
1861 ttgcagtgta cccagaactg tttagctaat attctatgtt taattaatga atactaactc
1921 taagaacccc tcactgattc actcaatagc atcttaagtg aaaaaccttc tattacatgc
1981 aaaaaatcat tgtttttaag ataacaaaag tagggaataa acaagctgaa cccactttta
2041 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa
```

[122] IL-17RB is encoded by the following amino acid sequence (NCBI Accession No. NM_018725 and SEQ ID NO: 16):

MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLIPGDLRDLRVEPVTTSVATGDYSILMNVS
WVLRADASIRLLKATKICVTGKSNFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGFPVELNTVYFIGA
HNIPNANMNEDGPSMSVNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKKNEETVEVNFTTTPLGN
RYMALIQHSTIIGFSQVFEPHQKKQTRASVVIPVTGDSEGATVQLTPYFPTCGSDCIRHKGTVVLCPQTG
VPFPLDNNKSKPGGWLPLLLLSLLVATWVLVAGIYLMWRHERIKKTSFSTTTLLPPIKVLVVYPSEICFH
HTICYFTEFLQNHCRSEVILEKWQKKKIAEMGPVQWLATQKKAADKVVFLLSNDVNSVCDGTCGKSE
GSPSENSQDLFPLAFNLFCSDLRSQIHLHKYVVVYFREIDTKDDYNALSVCPKYHLMKDATAFCAELLH
VKQQVSAGKRSQACHDGCCSL

[123] IL-17RC, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_153461 and SEQ ID NO: 17):

```
   1 aaaacgaaag cactccgtgc tggaagtagg aggagagtca ggactcccag gacagagagt
  61 gcacaaacta cccagcacag ccccctccgc cccctctgga ggctgaagag ggattccagc
 121 ccctgccacc cacagacacg ggctgactgg ggtgtctgcc ccccttgggg gggggcagca
 181 cagggcctca ggcctgggtg ccacctggca cctagaagAT Gcctgtgccc tggttcttgc
 241 tgtccttggc actgggccga agcccagtgg tcctttctct ggagaggctt gtggggcctc
 301 aggacgctac ccactgctct ccggtgagtc tggaaccctg gggagacgag gaaaggctca
 361 gggttcagtt tttggctcag caaagcctta gcctggctcc tgtcactgct gccactgcca
 421 gaactgccct gtctggtctg tctggtgctg atggtagaag agaagaacgg ggaaggggca
 481 agagctgggt ctgtctttct ctgggagggt ctgggaatac ggagccccag aaaaagggcc
 541 tctcctgccg cctctgggac agtgacatac tctgcctgcc tggggacatc gtgcctgctc
 601 cgggccccgt gctggcgcct acgcacctgc agacagagct ggtgctgagg tgccagaagg
 661 agaccgactg tgacctctgt ctgcgtgtgg ctgtccactt ggccgtgcat gggcactggg
 721 aagagcctga agatgaggaa aagtttggag gagcagctga ctcaggggtg gaggagccta
 781 ggaatgcctc tctccaggcc caagtcgtgc tctccttcca ggcctaccct actgcccgct
 841 gcgtcctgct ggaggtgcaa gtgcctgctg cccttgtgca gtttggtcag tctgtgggct
 901 ctgtggtata tgactgcttc gaggctgccc tagggagtga ggtacgaatc tggtcctata
 961 ctcagcccag gtacgagaag gaactcaacc acacacagca gctgcctgac tgcaggggc
1021 tcgaagtctg gaacagcatc ccgagctgct gggccctgcc ctggctcaac gtgtcagcag
1081 atggtgacaa cgtgcatctg gttctgaatg tctctgagga gcagcacttc ggcctctccc
1141 tgtactggaa tcaggtccag ggcccccaa aaccccggtg gcacaaaaac ctgactggac
1201 cgcagatcat taccttgaac cacacagacc tggttccctg cctctgtatt caggtgtggc
1261 ctctggaacc tgactccgtt aggacgaaca tctgcccctt cagggaggac ccccgcgcac
1321 accagaacct ctggcaagcc gcccgactgc gactgctgac cctgcagagc tggctgctgg
1381 acgcaccgtg ctcgctgccc gcagaagcgg cactgtgctg gcgggctccg ggtggggacc
1441 cctgccagcc actggtccca ccgctttcct gggagaacgt cactgtggac aaggttctcg
1501 agttcccatt gctgaaaggc caccctaacc tctgtgttca ggtgaacagc tcggagaagc
1561 tgcagctgca ggagtgcttg tgggctgact ccctggggcc tctcaaagac gatgtgctac
1621 tgttggagac acgaggcccc caggacaaca gatccctctg tgccttggaa cccagtggct
1681 gtacttcact acccagcaaa gcctccacga gggcagctcg ccttggagag tacttactac
1741 aagacctgca gtcaggccag tgtctgcagc tatgggacga tgacttggga gcgctatggg
1801 cctgccccat ggacaaatac atccacaagc gctgggccct cgtgtggctg gcctgcctac
1861 tctttgccgc tgcgctttcc ctcatcctcc ttctcaaaaa ggatcacgcg aaagggtggc
1921 tgaggctctt gaaacaggac gtccgctcgg gggcggccgc caggggccgc gcggctctgc
1981 tcctctactc agccgatgac tcgggtttcg agcgcctggt gggcgccctg gcgtcggccc
2041 tgtgccagct gccgctgcgc gtggccgtag acctgtggag ccgtcgtgaa ctgagcgcgc
2101 aggggcccgt ggcttggttt cacgcgcagc ggcgccagac cctgcaggag ggcggcgtgg
2161 tggtcttgct cttctctccc ggtgcggtgg cgctgtgcag cgagtggcta caggatgggg
2221 tgtccgggcc cggggcgcac ggcccgcacg acgccttccg cgcctcgctc agctgcgtgc
2281 tgcccgactt cttgcagggc cgggcgcccg gcagctacgt gggggcctgc ttcgacaggc
2341 tgctccaccc ggacgccgta cccgcccttt tccgcaccgt gcccgtcttc acactgccct
2401 cccaactgcc agacttcctg ggggccctgc agcagcctcg cgccccgcgt tccgggcggc
2461 tccaagagag agcggagcaa gtgtcccggg cccttcagcc agccctggat agctacttcc
2521 atcccccggg gactcccgcg ccgggacgcg gggtgggacc aggggcggga cctggggcgg
2581 gggacgggac ttaaataaag gcagacgctg tttttctacc catgtggccc aaaaaaaaaa
2641 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a
```

[124] IL-17RC, transcript variant 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_153461 and SEQ ID NO: 18):

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPVSLEPWGDEERLRVQFLAQQSLSLAPVTAATAR
TALSGLSGADGRREERGRGKSWVCLSLGGSGNTEPQKKGLSCRLWDSDILCLPGDIVPAPGPVLAPTHL
QTELVLRCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADSGVEEPRNASLQAQVVLSFQAYP
TARCVLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPDCRGLEVW
NSIPSCWALPWLNVSADGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDL
VPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLLTLQSWLLDAPCSLPAEAALCWRAPGG
DPCQPLVPPLSWENVTVDKVLEFPLLKGHPNLCVQVNSSEKLQLQECLWADSLGPLKDDVLLLETRGP
QDNRSLCALEPSGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWDDDLGALWACPMDKYIHKRWAL
VWLACLLFAAALSLILLLKKDHAKGWLRLLKQDVRSGAAARGRAALLLYSADDSGFERLVGALASAL
CQLPLRVAVDLWSRRELSAQGPVAWFHAQRRQTLQEGGVVVLLFSPGAVALCSEWLQDGVSGPGAH
GPHDAFRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPALFRTVPVFTLPSQLPDFLGALQQPRAP
RSGRLQERAEQVSRALQPALDSYFHPPGTPAPGRGVGPGAGPGAGDGT

[125] IL-17RC, transcript variant 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_153460 and SEQ ID NO: 19):

```
   1 aaaacgaaag cactccgtgc tggaagtagg aggagagtca ggactcccag gacagagagt
  61 gcacaaacta cccagcacag ccccctccgc cccctctgga ggctgaagag ggattccagc
 121 ccctgccacc cacagacacg ggctgactgg ggtgtctgcc ccccttgggg gggggcagca
 181 cagggcctca ggcctgggtg ccacctggca cctagaagAT Gcctgtgccc tggttcttgc
 241 tgtccttggc actgggccga agcccagtgg tcctttctct ggagaggctt gtggggcctc
 301 aggacgctac ccactgctct ccgggcctct cctgccgcct ctgggacagt gacatactct
 361 gcctgcctgg ggacatcgtg cctgctccgg gccccgtgct ggcgcctacg cacctgcaga
 421 cagagctggt gctgaggtgc cagaaggaga ccgactgtga cctctgtctg cgtgtggctg
 481 tccacttggc cgtgcatggg cactgggaag agcctgaaga tgaggaaaag tttggaggag
 541 cagctgactc aggggtggag gagcctagga atgcctctct ccaggcccaa gtcgtgctct
 601 ccttccaggc ctaccctact gcccgctgcg tcctgctgga ggtgcaagtg cctgctgccc
 661 ttgtgcagtt tggtcagtct gtgggctctg tggtatatga ctgcttcgag gctgccctag
 721 ggagtgaggt acgaatctgg tcctatactc agcccaggta cgagaaggaa ctcaaccaca
 781 cacagcagct gcctgactgc agggggctcg aagtctggaa cagcatcccg agctgctggg
 841 ccctgccctg gctcaacgtg tcagcagatg gtgacaacgt gcatctggtt ctgaatgtct
 901 ctgaggagca gcacttcggc ctctccctgt actggaatca ggtccagggc cccccaaaac
 961 cccggtggca caaaaacctg actggaccgc agatcattac cttgaaccac acagacctgg
1021 ttccctgcct ctgtattcag gtgtggcctc tggaacctga ctccgttagg acgaacatct
1081 gccccttcag ggaggacccc cgcgcacacc agaacctctg gcaagccgcc cgactgcgac
1141 tgctgaccct gcagagctgg ctgctggacg caccgtgctc gctgcccgca gaagcggcac
1201 tgtgctggcg ggctccgggt ggggacccct gccagccact ggtcccaccg ctttcctggg
1261 agaacgtcac tgtggacaag gttctcgagt tcccattgct gaaaggccac cctaacctct
1321 gtgttcaggt gaacagctcg gagaagctgc agctgcagga gtgcttgtgg gctgactccc
1381 tggggcctct caaagacgat gtgctactgt tggagacacg aggcccccag gacaacagat
1441 ccctctgtgc cttggaaccc agtggctgta cttcactacc cagcaaagcc tccacgaggg
1501 cagctcgcct tggagagtac ttactacaag acctgcagtc aggccagtgt ctgcagctat
1561 gggacgatga cttgggagcg ctatgggcct gccccatgga caaatacatc cacaagcgct
1621 gggccctcgt gtggctggcc tgcctactct ttgccgctgc gctttccctc atcctccttc
1681 tcaaaaagga tcacgcgaaa gggtggctga ggctcttgaa acaggacgtc cgctcggggg
1741 cggccgccag gggccgcgcg gctctgctcc tctactcagc cgatgactcg ggtttcgagc
1801 gcctggtggg cgccctggcg tcggccctgt gccagctgcc gctgcgcgtg gccgtagacc
1861 tgtggagccg tcgtgaactg agcgcgcagg ggcccgtggc ttggtttcac gcgcagcggc
1921 gccagaccct gcaggagggc ggcgtggtgg tcttgctctt ctctcccggt gcggtggcgc
1981 tgtgcagcga gtggctacag gatggggtgt ccgggcccgg ggcgcacggc ccgcacgacg
2041 ccttccgcgc ctcgctcagc tgcgtgctgc ccgacttctt gcagggccgg gcgcccggca
2101 gctacgtggg ggcctgcttc gacaggctgc tccacccgga cgccgtaccc gccctttcc
2161 gcaccgtgcc cgtcttcaca ctgccctccc aactgccaga cttcctgggg gccctgcagc
2221 agcctcgcgc cccgcgttcc gggcggctcc aagagagagc ggagcaagtg tcccgggccc
2281 ttcagccagc cctggatagc tacttccatc ccccggggac tcccgcgccg ggacgcgggg
```

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2341 tgggaccagg ggcgggacct ggggcggggg acgggactta aataaaggca gacgctgttt
2401 ttctacccat gtggcccaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2461 aaaaaaaaaa aaaaaaaa
```

[126] IL-17RC, transcript variant 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_153460 and SEQ ID NO: 20):

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSCRLWDSDILCLPGDIVPAPGPVLAPTHLQTEL
VLRCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADSGVEEPRNASLQAQVVLSFQAYPTARC
VLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPDCRGLEVWNSIPS
CWALPWLNVSADGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDLVPCLC
IQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLLTLQSWLLDAPCSLPAEAALCWRAPGGDPCQP
LVPPLSWENVTVDKVLEFPLLKGHPNLCVQVNSSEKLQLQECLWADSLGPLKDDVLLLETRGPQDNRS
LCALEPSGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWDDDLGALWACPMDKYIHKRWALVWLA
CLLFAAALSLILLLKKDHAKGWLRLLKQDVRSGAAARGRAALLLYSADDSGFERLVGALASALCQLPL
RVAVDLWSRRELSAQGPVAWFHAQRRQTLQEGGVVVLLFSPGAVALCSEWLQDGVSGPGAHGPHDA
FRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPALFRTVPVFTLPSQLPDFLGALQQPRAPRSGRL
QERAEQVSRALQPALDSYFHPPGTPAPGRGVGPGAGPGAGDGT

[127] IL-17RC, transcript variant 3, is encoded by the following mRNA sequence (NCBI Accession No. NM_032732 and SEQ ID NO: 21):

```
   1 aaaacgaaag cactccgtgc tggaagtagg aggagagtca ggactcccag gacagagagt
  61 gcacaaacta cccagcacag ccccctccgc cccctctgga ggctgaagag ggattccagc
 121 ccctgccacc cacagacacg ggctgactgg ggtgtctgcc ccccttgggg gggggcagca
 181 cagggcctca ggcctgggtg ccacctggca cctagaagAT Gcctgtgccc tggttcttgc
 241 tgtccttggc actgggccga agcccagtgg tcctttctct ggagaggctt gtggggcctc
 301 aggacgctac ccactgctct ccgggcctct cctgccgcct ctgggacagt gacatactct
 361 gcctgcctgg ggacatcgtg cctgctccgg gccccgtgct ggcgcctacg cacctgcaga
 421 cagagctggt gctgaggtgc cagaaggaga ccgactgtga cctctgtctg cgtgtggctg
 481 tccacttggc cgtgcatggg cactgggaag agcctgaaga tgaggaaaag tttggaggag
 541 cagctgactc aggggtggag gagcctagga atgcctctct ccaggcccaa gtcgtgctct
 601 ccttccaggc ctaccctact gcccgctgcg tcctgctgga ggtgcaagtg cctgctgccc
 661 ttgtgcagtt tggtcagtct gtgggctctg tggtatatga ctgcttcgag gctgccctag
 721 ggagtgaggt acgaatctgg tcctatactc agcccaggta cgagaaggaa ctcaaccaca
 781 cacagcagct gcctgccctg ccctggctca acgtgtcagc agatggtgac aacgtgcatc
 841 tggttctgaa tgtctctgag gagcagcact tcggcctctc cctgtactgg aatcaggtcc
 901 agggcccccc aaaaccccgg tggcacaaaa acctgactgg accgcagatc attaccttga
 961 accacacaga cctggttccc tgcctctgta ttcaggtgtg gcctctggaa cctgactccg
1021 ttaggacgaa catctgcccc ttcagggagg acccccgcgc acaccagaac ctctggcaag
1081 ccgcccgact gcgactgctg accctgcaga gctggctgct ggacgcaccg tgctcgctgc
1141 ccgcagaagc ggcactgtgc tggcgggctc cgggtgggga cccctgccag ccactggtcc
1201 caccgctttc ctgggagaac gtcactgtgg acaaggttct cgagttccca ttgctgaaag
1261 gccaccctaa cctctgtgtt caggtgaaca gctcggagaa gctgcagctg caggagtgct
1321 tgtgggctga ctccctgggg cctctcaaag acgatgtgct actgttggag acacgaggcc
1381 cccaggacaa cagatccctc tgtgccttgg aacccagtgg ctgtacttca ctacccagca
1441 aagcctccac gagggcagct cgccttggag agtacttact acaagacctg cagtcaggcc
1501 agtgtctgca gctatgggac gatgacttgg gagcgctatg ggcctgcccc atggacaaat
1561 acatccacaa gcgctgggcc ctcgtgtggc tggcctgcct actctttgcc gctgcgcttt
1621 ccctcatcct ccttctcaaa aaggatcacg cgaaagggtg gctgaggctc ttgaaacagg
1681 acgtccgctc gggggcggcc gccaggggcc gcgcggctct gctcctctac tcagccgatg
1741 actcgggttt cgagcgcctg gtgggcgccc tggcgtcggc cctgtgccag ctgccgctgc
1801 gcgtggccgt agacctgtgg agccgtcgtg aactgagcgc gcaggggccc gtggcttggt
1861 ttcacgcgca gcggcgccag accctgcagg agggcggcgt ggtggtcttg ctcttctctc
1921 ccggtgcggt ggcgctgtgc agcgagtggc tacaggatgg ggtgtccggg cccggggcgc
1981 acggcccgca cgacgccttc cgcgcctcgc tcagctgcgt gctgcccgac ttcttgcagg
2041 gccgggcgcc cggcagctac gtgggggcct gcttcgacag gctgctccac ccggacgccg
2101 tacccgccct tttccgcacc gtgcccgtct tcacactgcc ctcccaactg ccagacttcc
2161 tgggggccct gcagcagcct cgcgccccgc gttccgggcg gctccaagag agagcggagc
```

```
2221 aagtgtcccg ggcccttcag ccagccctgg atagctactt ccatcccccg gggactcccg
2281 cgccgggacg cggggtggga ccaggggcgg gacctggggc gggggacggg acttaaataa
2341 aggcagacgc tgtttttcta cccatgtggc ccaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2401 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa
```

[128] IL-17RC, transcript variant 3, is encoded by the following amino acid sequence (NCBI Accession No. NM_032732 and SEQ ID NO: 22):

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSCRLWDSDILCLPGDIVPAPGPVLAPTHLQTEL
VLRCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADSGVEEPRNASLQAQVVLSFQAYPTARC
VLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPALPWLNVSADGD
NVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDLVPCLCIQVWPLEPDSVRTNIC
PFREDPRAHQNLWQAARLRLLTLQSWLLDAPCSLPAEAALCWRAPGGDPCQPLVPPLSWENVTVDKV
LEFPLLKGHPNLCVQVNSSEKLQLQECLWADSLGPLKDDVLLLETRGPQDNRSLCALEPSGCTSLPSKA
STRAARLGEYLLQDLQSGQCLQLWDDDLGALWACPMDKYIHKRWALVWLACLLFAAALSLILLLKK
DHAKGWLRLLKQDVRSGAAARGRAALLLYSADDSGFERLVGALASALCQLPLRVAVDLWSRRELSA
QGPVAWFHAQRRQTLQEGGVVVLLFSPGAVALCSEWLQDGVSGPGAHGPHDAFRASLSCVLPDFLQG
RAPGSYVGACFDRLLHPDAVPALFRTVPVFTLPSQLPDFLGALQQPRAPRSGRLQERAEQVSRALQPAL
DSYFHPPGTPAPGRGVGPGAGPGAGDGT

[129] IL-17RD, transcript 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_001080973 and SEQ ID NO: 23):

```
   1 gcggccgccg cggccaccgc ccactcgggg ctggccagcg gcgggcggcc ggggcgcaga
  61 gaacggcctg gctgggcgag cgcacggccA TGgccccgtg gctgcagctc tgctccgtct
 121 tctttacggt caacgcctgc ctcaacggct cgcagctggc tgtggccgct ggcgggtccg
 181 gccgcgcgcg gggcgccgac acctgtggct ggaggggagt ggggccagcc agcagaaaca
 241 gtgggctgta caacatcacc ttcaaatatg acaattgtac cacctacttg aatccagtgg
 301 ggaagcatgt gattgctgac gcccagaata tcaccatcag ccagtatgct tgccatgacc
 361 aagtggcagt caccattctt tggtccccag gggccctcgg catcgaattc ctgaaaggat
 421 ttcgggtaat actggaggag ctgaagtcgg agggaagaca gtgccaacaa ctgattctaa
 481 aggatccgaa gcagctcaac agtagcttca aaagaactgg aatggaatct caacctttcc
 541 tgaatatgaa atttgaaacg gattatttcg taaaggttgt ccctttcct tccattaaaa
 601 acgaaagcaa ttaccaccct ttcttcttta gaacccgagc ctgtgacctg ttgttacagc
 661 cggacaatct agcttgtaaa cccttctgga agcctcggaa cctgaacatc agccagcatg
 721 gctcggacat gcaggtgtcc ttcgaccatg caccgcacaa cttcggcttc cgtttcttct
 781 atcttcacta caagctcaag cacgaaggac ctttcaagcg aaagacctgt aagcaggagc
 841 aaactacaga gacgaccagc tgcctccttc aaaatgtttc tccaggggat tatataattg
 901 agctggtgga tgacactaac acaacaagaa aagtgatgca ttatgcctta aagccagtgc
 961 actccccgtg ggccgggccc atcagagccg tggccatcac agtgccactg gtagtcatat
1021 cggcattcgc gacgctcttc actgtgatgt gccgcaagaa gcaacaagaa aatatatatt
1081 cacatttaga tgaagagagc tctgagtctt ccacatacac tgcagcactc ccaagagaga
1141 ggctccggcc gcggccgaag gtctttctct gctattccag taaagatggc cagaatcaca
1201 tgaatgtcgt ccagtgtttc gcctacttcc tccaggactt ctgtggctgt gaggtggctc
1261 tggacctgtg ggaagacttc agcctctgta gagaagggca gagagaatgg gtcatccaga
1321 agatccacga gtcccagttc atcattgtgg tttgttccaa aggtatgaag tactttgtgg
1381 acaagaagaa ctacaaacac aaaggaggtg gccgaggctc ggggaaagga gagctcttcc
1441 tggtggcggt gtcagccatt gccgaaaagc tccgccaggc caagcagagt tcgtccgcgg
1501 cgctcagcaa gtttatcgcc gtctactttg attattcctg cgagggagac gtccccggta
1561 tcctagacct gagtaccaag tacagactca tggacaatct tcctcagctc tgttcccact
1621 tgcactcccg agaccacggc ctccaggagc cggggcagca cacgcgacag ggcagcagaa
1681 ggaactactt ccggagcaag tcaggccggt ccctatacgt cgccatttgc aacatgcacc
1741 agtttattga cgaggagccc gactggttcg aaaagcagtt cgttcccttc catcctcctc
1801 cactgcgcta ccgggagcca gtcttggaga aatttgattc gggcttggtt ttaaatgatg
1861 tcatgtgcaa accagggcct gagagtgact tctgcctaaa ggtagaggcg gctgttcttg
1921 gggcaaccgg accagccgac tcccagcacg agagtcagca tgggggcctg gaccaagacg
1981 gggaggcccg gcctgccctt gacggtagcg ccgccctgca acccctgctg cacacggtga
2041 aagccggcag cccctcggac atgccgcggg actcaggcat ctatgactcg tctgtgccct
2101 catccgagct gtctctgcca ctgatggaag gactctcgac ggaccagaca gaaacgtctt
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2161 ccctgacgga gagcgtgtcc tcctcttcag gcctgggtga ggaggaacct cctgcccttc
2221 cttccaagct cctctcttct gggtcatgca aagcagatct tggttgccgc agctacactg
2281 atgaactcca cgcggtcgcc cctttgtaac aaaacgaaag agtctaagca ttgccacttt
2341 agctgctgcc tccctctgat tccccagctc atctccctgg ttgcatggcc cacttggagc
2401 tgaggtctca tacaaggata tttggagtga aatgctggcc agtacttgtt ctcccttgcc
2461 ccaacccttt accggatatc ttgacaaact ctccaatttt ctaaaatgat atggagctct
2521 gaaaggcatg tccataaggt ctgacaacag cttgccaaat ttggttagtc cttggatcag
2581 agcctgttgt gggaggtagg gaggaaatat gtaaagaaaa acaggaagat acctgcacta
2641 atcattcaga cttcattgag ctctgcaaac tttgcctgtt tgctattggc taccttgatt
2701 tgaaatgctt tgtgaaaaaa ggcactttta acatcatagc cacagaaatc aagtgccagt
2761 ctatctggaa tccatgttgt attgcagata atgttctcat ttatttttga tgtagaattt
2821 acattgccat gggtgttaaa taagctttga gtcaaaagtc aagaaagtga ctgaatatac
2881 agtcaccttt tatgaaatga gtctctgtgt tactgggtgg catgactgat tgaggtgaag
2941 ctcacggggc caggctgacc gtcttgaccg ttccacttga gataggttgg tcatcgtgca
3001 gaaggcccca ggacctcagc acacacagcc tcctcttggt ctgagtaggc atcatgtggg
3061 ggccagatct gcctgctgtt tccatgggtt acatttactg tgctgtatct cagatgttgg
3121 tgtctggaag tttattctta agagactgct acccagctgg tctgtattat tggaagttgc
3181 agttcgtgct ttggttggcc ttctggtcta aagctgtgtc ctgaatatta gggatcacaa
3241 ttcactgaaa tacagcagtg tgtggaggtg atggccagtt aatctgctga actggttttg
3301 actaatgaca aacctctttt taagatggta gaatggaggt gatagtcaca aaagtaaatg
3361 ttccattttt atgaatgact ttctacagag tttctatttc taaagaaaaa acaattgttc
3421 acatcccatc tgatgattag catgtgtgta atgaatgctg tcttggtctc ccctgtggaa
3481 acccttctcc ctgtgcctta gagcaggtgt gtacatctct cactaccttt ctcatgggtg
3541 ctgttagatt ttggcacccg ttttctcagc attcagccca gggaatgtgg ttttcacttc
3601 ttcgtcagat aagaccaaca tgaaggggta tgttgagaaa catcctgagg caaggtggga
3661 ggtgggatgg ggcaggactt tcccttccaa gcacatgcat ggcaggtggg gaaaggggg
3721 cttgcacccc tgctggaaag aaaaggtttg tgtatatttc tgatgcaaat gtcatactca
3781 ctgctctgta aaggcagctg gcagcttttt gggaaaagaa cgtgctcgtc tgttctctgg
3841 catcaagttt cttgcagctg ctctgaggga gagacagtga gctgcaagac tgcctcccca
3901 taacaacagg caactcagag aagagtcatt ttatgttgtt cctatggaat ctggaatgag
3961 tgcagagctc ctacccacac atgactgccc cgccatttca tcctaggcat tctgtgaagg
4021 agattggtta gtccaaactt gctaacatac gaaaattcac ttggaacatg atgagagatt
4081 tcttattgag gccaagagat gtttcctgtc ccagaggaac cattaggagt cgcttttagg
4141 gtattcagct ttgttcatga aataaggcat ctctgagaaa gtggccccag ggagagaatg
4201 gaggactggg aggagaagca ttaactgagc tccaagggtg tgtgggcaga gagcttgcta
4261 tgtgaactca ctccttaaga aaatggaaga gaaaaagaga gtgctagtta aaaaatcggg
4321 atgttttagt ttggatttag ggttttgata cttatgttga aatactaatg tttctgatca
4381 ataaaatcaa actcttaata taccgagtaa tgaaaccata gtgtgattgc ctcagaataa
4441 attgagaagt ccaacttcct agttttgttt aattagtttc acttttttcta ctctccccag
4501 tatgctagaa atgggaatcg ttgccctgca gattacggca aaacatctgt tttaagcaaa
4561 gctgcatttt ttgactcaga aattgtccca gacggtggat ataagatgaa attcagaaaa
4621 acgttctgcc aagtcacagg cttttagata ttatggaaac aagaaatgga aaacaggatg
4681 atctccatga gaggccttga tcctgagagt aaaaggcttg tgtagatagg ttagacaacg
4741 tcctctagaa aagagaccag ggataagtcc aggtttccag gaaaaccaag aagcctgcgg
4801 gtagctgaag gtagagtgct agttgttcat cttaacttac caatgagcta cagaaaggac
4861 ttagcatctg atgtcatcag ctttgccagg agagtgatca aggaggttaa agctcaggta
4921 aaggtgtgcc ttctcagaga ttggctacaa gcaacagaga ccacctcaac agagaccacc
4981 tcaacagact cagcccagcc atacaaggtg ccaaagctcc tccagagggc tgtcttgggc
5041 ctttgaggca attgatctcc agaaagagtc agaagtcatt ccagtccagg cccaggtatt
5101 cagatggtga cccagccaga taatagtatc ttgagcaaat aatagtatct tgagtgcaaa
5161 taagcaggaa gactgtcctt caaaaaatgt ggggttacat gattttcaga gccttttttt
5221 cagagttgag catcttttct tttaaaagaa ataaggggca agaggaccaa ttttattcct
5281 tgaggaaaaa tgacacaccc ttctcccaaa agaaagaaaa ctctctggcc ccccaacttc
5341 aacactaatt tggctccctg aagaagagag aaaatattat ttctgtcttt attgaagaga
5401 aatgggcaat gccaatgtga aggttactag tctttttttat tttctattgg tgaagactac
5461 tactgctctt atttagcaga tcttatacct tcagtggtca ccagtatagc aggtgaggta
5521 taaggaaaac agcagtgtga tgataaatgg taattaatat actttgtctg tgtcagcaat
5581 agggaatggt ggggactgtg gcaaactgaa gcgcccctgt tccacccaca gtgggtaatt
5641 ttccagtcga ctgtggccat gaagtacttc ctgatcttcc catttttcaa gaaaagctga
5701 caatctggat ttttatatga aaaattctga ttttaaaaaa tattggcaac taagttaaaa
5761 ttcaagtgaa tttagaccca gcagaagaca tggatggacc tgatttggtc cactgactac
5821 cagtttgtta acctgtgctt tataagattt gaaggaaagg cattcatggt aattacagac

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5881 ggtgccacca gaaaatgctc ttgctaaatg cagccagtag ttagattgct tctttctcca
5941 gtctcccccg caaagaaatt tgacgtgatt ctgaatgcac tggacatgtc ttgattgcgt
6001 ctttacattt cacagtgtct taaaagaaag gcaagccagt tgttaatttc agaatcagat
6061 ttatgctctc tcaatttaaa aaatgctggg aacaatttca ttttttttt tttgagatgg
6121 agtcttgctc tgttgcccag gctggagtgc agtggcgtga tctcggctca ctgcaagctc
6181 cacctcccgg gttcacgcca ttctcctgcc tcagcctcct gagtagctgg gactacaggc
6241 gcccaccacc acgcctggct aatttttttg tatttttagt agagacgggg tttcactgtg
6301 ttagccagga tgatctcgat ctcctgacct ggtgatccgc ttgcctcggc ctcccaaagt
6361 gctgggatta caggcgtgag ccactgcgcc cggcctaaca atttcattta aactccacaa
6421 cctaaagggc tttgtttata gttttagctc ttggcataat ttttttcagg tggtgtgcaa
6481 ttctgagcat aggccaagac atgattagga aagcaggcag ttgtagagag taaggcaagg
6541 aacctcctag cgtccattag agccaggtat ttgcattatc ttccgtttta agtggtctgt
6601 gaattgactg tgttttggag gtgtgaaaca gtatacagag aaaagctttt cctgatactg
6661 agatatcagt taggagtcca aatggggtgt tgggtcatcc ttgccatatc acctcctttc
6721 caggctcaga gtgaaaatag acaaaaggaa atctgactgc aagccagtgg ctttgattcc
6781 agtttcagag tttagggact aggagagagt ttagattatc tagcatattc tccccctggt
6841 gtcagacagg gctgtgcctg aattattcca gacatatggc tgtagatggt attctttatt
6901 ttataagaag gagattctgt aacctaccct gctgatcaga tagttctttg tatgtcttag
6961 agaaattcaa gccagcttcc ttttgttcgg cttgtagtgg agaaagaaca gctggtcacc
7021 ttccatgtat tcaaaaacca cagtgaagtc atccccctgg tgtttttatt tcagtgataa
7081 ataattccac ccacttaaac cattcttcat ggctcttgtt ttccaggggc ctaataattt
7141 tcactgctgt aatgtttctc agcttcacac ttagtttagt tgcccaaaca atgttggtgc
7201 cttactcaca ttggtgcctt gtgaagacga ggctcaggat ggggattatg gggaaattct
7261 tgcacaccca gctcctctta ccacttaaaa atataatggc actttcacaa aatgatatgt
7321 cacctatatt cattgagaat tatttgactg ccacattttt cccctgatga tagtcatcta
7381 tcataacttg tgtttgtttt cctcctgaga tcaaacactt ggtgcttatt cctgatgtat
7441 actctgagac cagctcttac cttctgagtg gcagctaccc ctccctccca attttagatc
7501 ctatttttac acatctctat agatatcacc tttatttcat gactcacaat attaaatggt
7561 acagacttca gtttaaccac tggtgtggta acagcagtag ttgctaagta ccaccttccc
7621 attgctgttt gagggctaat ttgcaaagac atttgaatct cccagtgaag atgtctgggg
7681 aattttggcc agttgtcttc cctcttgccc ttttgttctt taaaattcag cttggaccat
7741 agacacctcc aggatcttgt ttatgttctg ctctcaattg accaagcact gcgttttgca
7801 caatcagaag tctcacaaaa gcaaacagtt atgactgcat atctgatgtt tatatcctat
7861 aaaatttcag gaagattcag agtcaatctt ctatttgtac atgatgtaga caaaattagc
7921 tgctccaatt gttagacaaa aaattgccat tggattacac taatgtgctc atctgttgtt
7981 ttaaaagttt ggtatcaggc ggggcacggt ggctcacgcc tgtaatccca gcattttggg
8041 aggccaaggt gggcggatca cctgaggtcc agagttcaag accagcctga ccaacatggt
8101 gaaaccctgt ctctactaaa aatacaaaat taatcaggcg tggttgtgtg tgcctgtaat
8161 cccagctact cgagaggctg aggcaggaga atcgcttgaa tccgggaggc agaggttgca
8221 gtgagctgag atcacgccat tgcactctag cctgggcaac aagagcgaaa ctccgtctca
8281 acaacaacaa caaaaagttt ggtatgtttc tctcaagaaa aaagcatggt gagtccagac
8341 agcagcaaaa gcttttgtga aaaccaattg tgttcatcta gatagtaagt aactcctatt
8401 tttactgtta atttttaaa agagaatttt tccctgtgga aactccctgt tagtacgtcc
8461 taggggagaa agcctgtgga atatggtggt tattgatggc gttgcctttg tttcatcttt
8521 gagtttgccc tttgtgggat ctagtgggat aatgagcact gacagaactc ttaacagcgt
8581 gctgtatttt tgacattgaa aatgttaatg acttgatttg tacataactc tgtaactagg
8641 tgaaagtaga tcacagctga catttacaaa atgtttttgt accttagaat ttctgcatta
8701 aataaaatgt tttgttttaa
```

[130] IL-17RD, transcript 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_001080973 and SEQ ID NO: 24):

MAPWLQLCSVFFTVNACLNGSQLAVAAGGSGRARGADTCGWRGVGPASRNSGLYNITFKYDNCTTY
LNPVGKHVIADAQNITISQYACHDQVAVTILWSPGALGIEFLKGFRVILEELKSEGRQCQQLILKDPKQL
NSSFKRTGMESQPFLNMKFETDYFVKVVPFPSIKNESNYHPFFFRTRACDLLLQPDNLACKPFWKPRNL
NISQHGSDMQVSFDHAPHNFGFRFFYLHYKLKHEGPFKRKTCKQEQTTETTSCLLQNVSPGDYIIELVD
DTNTTRKVMHYALKPVHSPWAGPIRAVAITVPLVVISAFATLFTVMCRKKQQENIYSHLDEESSESSTY
TAALPRERLRPRPKVFLCYSSKDGQNHMNVVQCFAYFLQDFCGCEVALDLWEDFSLCREGQREWVIQ
KIHESQFIIVVCSKGMKYFVDKKNYKHKGGGRGSGKGELFLVAVSAIAEKLRQAKQSSSAALSKFIAVY
FDYSCEGDVPGILDLSTKYRLMDNLPQLCSHLHSRDHGLQEPGQHTRQGSRRNYFRSKSGRSLYVAIC
NMHQFIDEEPDWFEKQFVPFHPPPLRYREPVLEKFDSGLVLNDVMCKPGPESDFCLKVEAAVLGATGP

ADSQHESQHGGLDQDGEARPALDGSAALQPLLHTVKAGSPSDMPRDSGIYDSSVPSSELSLPLMEGLST
DQTETSSLTESVSSSSGLGEEEPPALPSKLLSSGSCKADLGCRSYTDELHAVAPL

[131] IL-17RD, transcript 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_017563 and SEQ ID NO: 25, note that this sequence contains an alternative start codon from nucleotide position 208-210):

```
   1 atccgctctt cttttcctcc gggaaaagaa acgggaagtg gccgtgggcc ggtgaattcc
  61 gtgtagtggc caagctttgt tccaaagagg gggaggtggt gacagtctct tgcccactga
 121 agcgtgccag acagagtgct aggcatgggg gcagaggtga atcagatgac agccacctct
 181 caccacgagg agtggctgaa agtgtgaCTG gactacaggc aatcctggcc ttggcaggga
 241 gtggggccag ccagcagaaa cagtgggctg tacaacatca ccttcaaata tgacaattgt
 301 accacctact tgaatccagt ggggaagcat gtgattgctg acgcccagaa tatcaccatc
 361 agccagtatg cttgccatga ccaagtggca gtcaccattc tttggtcccc aggggccctc
 421 ggcatcgaat tcctgaaagg atttcgggta atactggagg agctgaagtc ggagggaaga
 481 cagtgccaac aactgattct aaaggatccg aagcagctca acagtagctt caaaagaact
 541 ggaatggaat ctcaaccttt cctgaatatg aaatttgaaa cggattattt cgtaaaggtt
 601 gtccctttc cttccattaa aaacgaaagc aattaccacc ctttcttctt tagaacccga
 661 gcctgtgacc tgttgttaca gccggacaat ctagcttgta aacccttctg gaagcctcgg
 721 aacctgaaca tcagccagca tggctcggac atgcaggtgt ccttcgacca tgcaccgcac
 781 aacttcggct tccgtttctt ctatcttcac tacaagctca agcacgaagg acctttcaag
 841 cgaaagacct gtaagcagga gcaaactaca gagacgacca gctgcctcct tcaaaatgtt
 901 tctccagggg attatataat tgagctggtg gatgacacta acacaacaag aaaagtgatg
 961 cattatgcct taaagccagt gcactccccg tgggccgggc ccatcagagc cgtggccatc
1021 acagtgccac tggtagtcat atcggcattc gcgacgctct tcactgtgat gtgccgcaag
1081 aagcaacaag aaaatatata ttcacattta gatgaagaga gctctgagtc ttccacatac
1141 actgcagcac tcccaagaga gaggctccgg ccgcggccga aggtctttct ctgctattcc
1201 agtaaagatg gccagaatca catgaatgtc gtccagtgtt tcgcctactt cctccaggac
1261 ttctgtggct gtgaggtggc tctggacctg tgggaagact tcagcctctg tagagaaggg
1321 cagagagaat gggtcatcca gaagatccac gagtcccagt tcatcattgt ggtttgttcc
1381 aaaggtatga agtactttgt ggacaagaag aactacaaac acaaaggagg tggccgaggc
1441 tcggggaaag gagagctctt cctggtggcg gtgtcagcca ttgccgaaaa gctccgccag
1501 gccaagcaga gttcgtccgc ggcgctcagc aagtttatcg ccgtctactt tgattattcc
1561 tgcgagggag acgtccccgg tatcctagac ctgagtacca agtacagact catggacaat
1621 cttcctcagc tctgttccca cttgcactcc cgagaccacg gcctccagga gccggggcag
1681 cacacgcgac agggcagcag aaggaactac ttccggagca agtcaggccg gtccctatac
1741 gtcgccattt gcaacatgca ccagtttatt gacgaggagc ccgactggtt cgaaaagcag
1801 ttcgttccct tccatcctcc tccactgcgc taccgggagc cagtcttgga gaaatttgat
1861 tcgggcttgg ttttaaatga tgtcatgtgc aaaccagggc ctgagagtga cttctgccta
1921 aaggtagagg cggctgttct tggggcaacc ggaccagccg actcccagca cgagagtcag
1981 catgggggcc tggaccaaga cggggaggcc cggcctgccc ttgacggtag cgccgccctg
2041 caacccctgc tgcacacggt gaaagccggc agcccctcgg acatgccgcg ggactcaggc
2101 atctatgact cgtctgtgcc ctcatccgag ctgtctctgc cactgatgga aggactctcg
2161 acggaccaga cagaaacgtc ttccctgacg gagagcgtgt cctcctcttc aggcctgggt
2221 gaggaggaac ctcctgccct tccttccaag ctcctctctt ctgggtcatg caaagcagat
2281 cttggttgcc gcagctacac tgatgaactc cacgcggtcg ccccctttgta acaaaacgaa
2341 agagtctaag cattgccact ttagctgctg cctccctctg attccccagc tcatctccct
2401 ggttgcatgg cccacttgga gctgaggtct catacaagga tatttggagt gaaatgctgg
2461 ccagtacttg ttctcccttg ccccaaccct ttaccggata tcttgacaaa ctctccaatt
2521 ttctaaaatg atatggagct ctgaaaggca tgtccataag gtctgacaac agcttgccaa
2581 atttggttag tccttggatc agagcctgtt gtgggaggta gggaggaaat atgtaaagaa
2641 aaacaggaag atacctgcac taatcattca gacttcattg agctctgcaa actttgcctg
2701 tttgctattg gctaccttga tttgaaatgc tttgtgaaaa aaggcacttt taacatcata
2761 gccacagaaa tcaagtgcca gtctatctgg aatccatgtt gtattgcaga taatgttctc
2821 atttattttt gatgtagaat ttacattgcc atgggtgtta aataagcttt gagtcaaaag
2881 tcaagaaagt gactgaatat acagtcacct tttatgaaat gagtctctgt gttactgggt
2941 ggcatgactg attgaggtga agctcacggg gccaggctga ccgtcttgac cgttccactt
3001 gagataggtt ggtcatcgtg cagaaggccc caggacctca gcacacacag cctcctcttg
3061 gtctgagtag gcatcatgtg ggggccagat ctgcctgctg tttccatggg ttacatttac
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3121 tgtgctgtat ctcagatgtt ggtgtctgga agtttattct taagagactg ctacccagct
3181 ggtctgtatt attggaagtt gcagttcgtg ctttggttgg ccttctggtc taaagctgtg
3241 tcctgaatat tagggatcac aattcactga aatacagcag tgtgtggagg tgatggccag
3301 ttaatctgct gaactggttt tgactaatga caaacctctt tttaagatgg tagaatggag
3361 gtgatagtca caaaagtaaa tgttccattt ttatgaatga ctttctacag agtttctatt
3421 tctaaagaaa aaacaattgt tcacatccca tctgatgatt agcatgtgtg taatgaatgc
3481 tgtcttggtc tcccctgtgg aaacccttct ccctgtgcct tagagcaggt gtgtacatct
3541 ctcactacct ttctcatggg tgctgttaga ttttggcacc cgttttctca gcattcagcc
3601 cagggaatgt ggttttcact tcttcgtcag ataagaccaa catgaagggg tatgttgaga
3661 aacatcctga ggcaaggtgg gaggtgggat ggggcaggac tttcccttcc aagcacatgc
3721 atggcaggtg gggaaagggg ggcttgcacc cctgctggaa agaaaaggtt tgtgtatatt
3781 tctgatgcaa atgtcatact cactgctctg taaaggcagc tggcagcttt ttgggaaaag
3841 aacgtgctcg tctgttctct ggcatcaagt ttcttgcagc tgctctgagg gagagacagt
3901 gagctgcaag actgcctccc cataacaaca ggcaactcag agaagagtca ttttatgttg
3961 ttcctatgga atctggaatg agtgcagagc tcctacccac acatgactgc cccgccattt
4021 catcctaggc attctgtgaa ggagattggt tagtccaaac ttgctaacat acgaaaattc
4081 acttggaaca tgatgagaga tttcttattg aggccaagag atgtttcctg tcccagagga
4141 accattagga gtcgctttta gggtattcag ctttgttcat gaaataaggc atctctgaga
4201 aagtggcccc agggagagaa tggaggactg ggaggagaag cattaactga gctccaaggg
4261 tgtgtgggca gagagcttgc tatgtgaact cactccttaa gaaaatggaa gagaaaaaga
4321 gagtgctagt taaaaaatcg ggatgtttta gtttggattt agggttttga tacttatgtt
4381 gaaatactaa tgtttctgat caataaaatc aaactcttaa tataccgagt aatgaaacca
4441 tagtgtgatt gcctcagaat aaattgagaa gtccaacttc ctagttttgt ttaattagtt
4501 tcacttttttc tactctcccc agtatgctag aaatgggaat cgttgccctg cagattacgg
4561 caaaacatct gttttaagca aagctgcatt ttttgactca gaaattgtcc cagacggtgg
4621 atataagatg aaattcagaa aaacgttctg ccaagtcaca ggcttttaga tattatggaa
4681 acaagaaatg gaaaacagga tgatctccat gagaggcctt gatcctgaga gtaaaaggct
4741 tgtgtagata ggttagacaa cgtcctctag aaaagagacc agggataagt ccaggtttcc
4801 aggaaaacca agaagcctgc gggtagctga aggtagagtg ctagttgttc atcttaactt
4861 accaatgagc tacagaaagg acttagcatc tgatgtcatc agctttgcca ggagagtgat
4921 caaggaggtt aaagctcagg taaaggtgtg ccttctcaga gattggctac aagcaacaga
4981 gaccacctca acagagacca cctcaacaga ctcagcccag ccatacaagg tgccaaagct
5041 cctccagagg gctgtcttgg gcctttgagg caattgatct ccagaaagag tcagaagtca
5101 ttccagtcca ggcccaggta ttcagatggt gacccagcca gataatagta tcttgagcaa
5161 ataatagtat cttgagtgca aataagcagg aagactgtcc ttcaaaaaat gtggggttac
5221 atgattttca gagcctttt ttcagagttg agcatctttt cttttaaaag aaataagggg
5281 caagaggacc aattttattc cttgaggaaa aatgacacac ccttctccca aaagaaagaa
5341 aactctctgg ccccccaact tcaacactaa tttggctccc tgaagaagag agaaaatatt
5401 atttctgtct ttattgaaga gaaatgggca atgccaatgt gaaggttact agtctttttt
5461 attttctatt ggtgaagact actactgctc ttatttagca gatcttatac cttcagtggt
5521 caccagtata gcaggtgagg tataaggaaa acagcagtgt gatgataaat ggtaattaat
5581 atactttgtc tgtgtcagca atagggaatg gtggggactg tggcaaactg aagcgccccc
5641 gttccaccca cagtgggtaa ttttccagtc gactgtggcc atgaagtact tcctgatctt
5701 cccatttttc aagaaaagct gacaatctgg atttttatat gaaaaattct gattttaaaa
5761 aatattggca actaagttaa aattcaagtg aatttagacc cagcagaaga catggatgga
5821 cctgatttgg tccactgact accagtttgt taacctgtgc tttataagat ttgaaggaaa
5881 ggcattcatg gtaattacag acggtgccac cagaaaatgc tcttgctaaa tgcagccagt
5941 agttagattg cttctttctc cagtctcccc cgcaaagaaa tttgacgtga ttctgaatgc
6001 actggacatg tcttgattgc gtctttacat ttcacagtgt cttaaaagaa aggcaagcca
6061 gttgttaatt tcagaatcag atttatgctc tctcaattta aaaaatgctg ggaacaattt
6121 catttttttt tttttgagat ggagtcttgc tctgttgccc aggctggagt gcagtggcgt
6181 gatctcggct cactgcaagc tccacctccc gggttcacgc cattctcctg cctcagcctc
6241 ctgagtagct gggactacag gcgcccacca ccacgcctgg ctaatttttt tgtattttta
6301 gtagagacgg ggtttcactg tgttagccag gatgatctcg atctcctgac ctggtgatcc
6361 gcttgcctcg gcctcccaaa gtgctgggat tacaggcgtg agccactgcg cccggcctaa
6421 caatttcatt taaactccac aacctaaagg gctttgttta tagtttagc tcttggcata
6481 atttttttca ggtggtgtgc aattctgagc ataggccaag acatgattag gaaagcaggc
6541 agttgtagag agtaaggcaa ggaacctcct agcgtccatt agagccaggt atttgcatta
6601 tcttccgttt taagtggtct gtgaattgac tgtgttttgg aggtgtgaaa cagtatacag
6661 agaaaagctt ttcctgatac tgagatatca gttaggagtc caaatggggt gttgggtcat
6721 ccttgccata tcacctcctt tccaggctca gagtgaaaat agacaaaagg aaatctgact
6781 gcaagccagt ggctttgatt ccagtttcag agtttaggga ctaggagaga gtttagatta

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6841 tctagcatat tctccccctg gtgtcagaca gggctgtgcc tgaattattc cagacatatg
6901 gctgtagatg gtattcttta ttttataaga aggagattct gtaacctacc ctgctgatca
6961 gatagttctt tgtatgtctt agagaaattc aagccagctt ccttttgttc ggcttgtagt
7021 ggagaaagaa cagctggtca ccttccatgt attcaaaaac cacagtgaag tcatcccccc
7081 ggtgttttta tttcagtgat aaataattcc acccacttaa accattcttc atggctcttg
7141 ttttccaggg gcctaataat tttcactgct gtaatgtttc tcagcttcac acttagttta
7201 gttgcccaaa caatgttggt gccttactca cattggtgcc ttgtgaagac gaggctcagg
7261 atggggatta tggggaaatt cttgcacacc cagctcctct taccacttaa aaatataatg
7321 gcactttcac aaaatgatat gtcacctata ttcattgaga attatttgac tgccacattt
7381 ttcccctgat gatagtcatc tatcataact tgtgtttgtt ttcctcctga gatcaaacac
7441 ttggtgctta ttcctgatgt atactctgag accagctctt accttctgag tggcagctac
7501 ccctccctcc caattttaga tcctattttt acacatctct atagatatca cctttatttc
7561 atgactcaca atattaaatg gtacagactt cagtttaacc actggtgtgg taacagcagt
7621 agttgctaag taccaccttc ccattgctgt ttgagggcta atttgcaaag acatttgaat
7681 ctcccagtga agatgtctgg ggaattttgg ccagttgtct tccctcttgc ccttttgttc
7741 tttaaaattc agcttggacc atagacacct ccaggatctt gtttatgttc tgctctcaat
7801 tgaccaagca ctgcgttttg cacaatcaga agtctcacaa aagcaaacag ttatgactgc
7861 atatctgatg tttatatcct ataaaatttc aggaagattc agagtcaatc ttctatttgt
7921 acatgatgta gacaaaatta gctgctccaa ttgttagaca aaaaattgcc attggattac
7981 actaatgtgc tcatctgttg ttttaaaagt ttggtatcag gcggggcacg gtggctcacg
8041 cctgtaatcc cagcattttg ggaggccaag gtgggcggat cacctgaggt ccagagttca
8101 agaccagcct gaccaacatg gtgaaaccct gtctctacta aaaatacaaa attaatcagg
8161 cgtggttgtg tgtgcctgta atcccagcta ctcgagaggc tgaggcagga gaatcgcttg
8221 aatccgggag gcagaggttg cagtgagctg agatcacgcc attgcactct agcctgggca
8281 acaagagcga aactccgtct caacaacaac aacaaaaagt ttggtatgtt tctctcaaga
8341 aaaaagcatg gtgagtccag acagcagcaa aagcttttgt gaaaaccaat tgtgttcatc
8401 tagatagtaa gtaactccta tttttactgt taatttttta aaagagaatt tttccctgtg
8461 gaaactccct gttagtacgt cctaggggag aaagcctgtg gaatatggtg gttattgatg
8521 gcgttgcctt tgtttcatct ttgagtttgc cctttgtggg atctagtggg ataatgagca
8581 ctgacagaac tcttaacagc gtgctgtatt tttgacattg aaaatgttaa tgacttgatt
8641 tgtacataac tctgtaacta ggtgaaagta gatcacagct gacatttaca aaatgttttt
8701 gtaccttaga atttctgcat taaataaaat gttttgtttt aa
```

[132] IL-17RD, transcript 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_017563 and SEQ ID NO: 26):

MDYRQSWPWQGVGPASRNSGLYNITFKYDNCTTYLNPVGKHVIADAQNITISQYACHDQVAVTILWS
PGALGIEFLKGFRVILEELKSEGRQCQQLILKDPKQLNSSFKRTGMESQPFLNMKFETDYFVKVVPFPSI
KNESNYHPFFFRTRACDLLLQPDNLACKPFWKPRNLNISQHGSDMQVSFDHAPHNFGFRFFYLHYKLK
HEGPFKRKTCKQEQTTETTSCLLQNVSPGDYIIELVDDTNTTRKVMHYALKPVHSPWAGPIRAVAITVP
LVVISAFATLFTVMCRKKQQENIYSHLDEESSESSTYTAALPRERLRPRPKVFLCYSSKDGQNHMNVVQ
CFAYFLQDFCGCEVALDLWEDFSLCREGQREWVIQKIHESQFIIVVCSKGMKYFVDKKNYKHKGGGR
GSGKGELFLVAVSAIAEKLRQAKQSSSAALSKFIAVYFDYSCEGDVPGILDLSTKYRLMDNLPQLCSHL
HSRDHGLQEPGQHTRQGSRRNYFRSKSGRSLYVAICNMHQFIDEEPDWFEKQFVPFHPPPLRYREPVLE
KFDSGLVLNDVMCKPGPESDFCLKVEAAVLGATGPADSQHESQHGGLDQDGEARPALDGSAALQPLL
HTVKAGSPSDMPRDSGIYDSSVPSSELSLPLMEGLSTDQTETSSLTESVSSSSGLGEEEPPALPSKLLSSGS
CKADLGCRSYTDELHAVAPL

[133] IL-17RE, transcript variant 1, is encoded by the following mRNA sequence (NCBI Accession No. NM_153480 and SEQ ID NO: 27):

```
   1 cgagggctcc tgctggtact gtgttcgctg ctgcacagca aggccctgcc acccaccttc
  61 aggccatgca gccatgttcc gggagcccta attgcacaga agcccATGgg gagctccaga
 121 ctggcagccc tgctcctgcc tctcctcctc atagtcatcg acctctctga ctctgctggg
 181 attggctttc gccacctgcc ccactggaac acccgctgtc ctctggcctc ccacacggat
 241 gacagtttca ctggaagttc tgcctatatc ccttgccgca cctggtgggc cctcttctcc
 301 acaaagcctt ggtgtgtgcg agtctggcac tgttcccgct gtttgtgcca gcatctgctg
 361 tcaggtggct caggtcttca acggggcctc ttccacctcc tggtgcagaa atccaaaaag
 421 tcttccacat tcaagttcta taggagacac aagatgccag cacctgctca gaggaagctg
 481 ctgcctcgtc gtcacctgtc tgagaagagc catcacattt ccatcccctc cccagacatc
```

```
 541 tcccacaagg gacttcgctc taaaaggacc caaccttcgg atccagagac atgggaaagt
 601 cttcccagat tggactcaca aaggcatgga ggacccgagt tctcctttga tttgctgcct
 661 gaggcccggg ctattcgggt gaccatatct tcaggccctg aggtcagcgt gcgtctttgt
 721 caccagtggg cactggagtg tgaagagctg agcagtccct atgatgtcca gaaaattgtg
 781 tctgggggcc acactgtaga gctgccttat gaattccttc tgccctgtct gtgcatagag
 841 gcatcctacc tgcaagagga cactgtgagg cgcaaaaaat gtcccttcca gagctggcca
 901 gaagcctatg gctcggactt ctggaagtca gtgcacttca ctgactacag ccagcacact
 961 cagatggtca tggccctgac actccgctgc ccactgaagc tggaagctgc cctctgccag
1021 aggcacgact ggcataccct ttgcaaagac ctcccgaatg ccacagctcg agagtcagat
1081 gggtggtatg ttttggagaa ggtggacctg cacccccagc tctgcttcaa gttctctttt
1141 ggaaacagca gccatgttga atgcccccac cagactgggt ctctcacatc ctggaatgta
1201 agcatggata cccaagccca gcagctgatt cttcacttct cctcaagaat gcatgccacc
1261 ttcagtgctg cctggagcct cccaggcttg gggcaggaca ctttggtgcc ccccgtgtac
1321 actgtcagcc aggcccgggg ctcaagccca gtgtcactag acctcatcat tcccttcctg
1381 aggccagggt gctgtgtcct ggtgtggcgg tcagatgtcc agtttgcctg gaagcacctc
1441 ttgtgtccgg atgtctctta cagacacctg gggctcttga tcctggcact gctggccctc
1501 ctcaccctac tgggtgttgt tctggccctc acctgccggc gcccacagtc aggcccgggc
1561 ccagcgcggc cagtgctcct cctgcacgcg gcggactcgg aggcgcagcg gcgcctggtg
1621 ggagcgctgg ctgaactgct acgggcagcg ctgggcggcg ggcgcgacgt gatcgtggac
1681 ctgtgggagg ggaggcacgt ggcgcgcgtg ggcccgctgc cgtggctctg ggcggcgcgg
1741 acgcgcgtag cgcgggagca gggcactgtg ctgctgctgt ggagcggcgc cgaccttcgc
1801 ccggtcagcg gccccgaccc ccgcgccgcg cccctgctcg ccctgctcca cgctgccccg
1861 cgcccgctgc tgctgctcgc ttacttcagt cgcctctgcg ccaagggcga catccccccg
1921 ccgctgcgcg ccctgccgcg ctaccgcctg ctgcgcgacc tgccgcgtct gctgcgggcg
1981 ctggacgcgc ggcctttcgc agaggccacc agctggggcc gccttggggc gcggcagcgc
2041 aggcagagcc gcctagagct gtgcagccgg ctcgaacgag aggccgcccg acttgcagac
2101 ctaggttgag cagagctcca ccgcagtccc gggtgtctgc ggccgcaacg caacggacac
2161 tggctggaac cccggaatga gccttcgacc ctgaaatcct tggggtgcct cgaggacgac
2221 tggccgaaaa gccgcattcc ctgcctcaca ggccggaagt cccagcccag tccccgcgcg
2281 cgtccctctt cctcctcata ctttcccttg actgagagct cctctaaccc ctgttctgat
2341 gggggagggc ggtcttccca cttcctctcc agaactccag aaagagcagt gtgcttatgc
2401 ttcagtccag gctggagagg ttggggccgg ggtagggagg caggagccat gtcagttctg
2461 aaggagggtg aggcggtggg ggattgcagg gggcggctga gagaaaacct ccttgggggc
2521 cagggattcc ctttcccact ctgaggctct ggccagaggg agagaggact ctggacctag
2581 gaaaagaggc ttttggctcc aggtggtcag gacagtgggg gttgggggtg gggtgggtgg
2641 gtgctggcgg tggggaccaa gatccggaaa gatgaataaa gacaaacatg acaaactaag
2701 aaaaaaaaaa aaaaaaa
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[134] IL-17RE, transcript variant 1, is encoded by the following amino acid sequence (NCBI Accession No. NM_153480 and SEQ ID NO: 28):

```
MGSSRLAALLLPLLLIVIDLSDSAGIGFRHLPHWNTRCPLASHTDDSFTGSSAYIPCRTWWALFSTKPWCVRVWH
CSRCLCQHLLSGGSGLQRGLFHLLVQKSKKSSTFKFYRRHKMPAPAQRKLLPRRHLSEKSHHISIPSPDISHKGL
RSKRTQPSDPETWESLPRLDSQRHGGPEFSFDLLPEARAIRVTISSGPEVSVRLCHQWALECEELSSPYDVQKIV
SGGHTVELPYEFLLPCLCIEASYLQEDTVRRKKCPFQSWPEAYGSDFWKSVHFTDYSQHTQMVMALTLRCPLKLE
AALCQRHDWHTLCKDLPNATARESDGWYVLEKVDLHPQLCFKFSFGNSSHVECPHQTGSLTSWNVSMDTQAQQLI
LHFSSRMHATFSAAWSLPGLGQDTLVPPVYTVSQARGSSPVSLDLIIPFLRPGCCVLVWRSDVQFAWKHLLCPDV
SYRHLGLLILALLALLTLLGVVLALTCRRPQSGPGPARPVLLLHAADSEAQRRLVGALAELLRAALGGGRDVIVD
LWEGRHVARVGPLPWLWAARTRVAREQGTVLLLWSGADLRPSGPDPRAAPLLALLHAAPRPLLLLAYFSRLCAKG
DIPPPLRALPRYRLLRDLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLEREAARLADLG
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[135] IL-17RE, transcript variant 2, is encoded by the following mRNA sequence (NCBI Accession No. NM_153481 and SEQ ID NO: 29):

```
   1 cgagggctcc tgctggtact gtgttcgctg ctgcacagca aggccctgcc acccaccttc
  61 aggccatgca gccatgttcc gggagcccta attgcacaga agcccatggg gagctccaga
 121 ctggcagccc tgctcctgcc tctcctcctc atagtcatcg acctctctga ctctgctggg
 181 attggctttc gccacctgcc ccactggaac acccgctgtc ctctggcctc ccacacggtc
 241 ttcaacgggg cctcttccac ctcctggtgc agaaatccaa aaagtcttcc acattcaagt
 301 tctataggag acacaagATG ccagcacctg ctcagaggaa gctgctgcct cgtcgtcacc
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 361 tgtctgagaa gagccatcac atttccatcc cctccccaga catctcccac aagggacttc
 421 gctctaaaag gacccaacct tcggatccag agacatggga aagtcttccc agattggact
 481 cacaaaggca tggaggaccc gagttctcct ttgatttgct gcctgaggcc cgggctattc
 541 gggtgaccat atcttcaggc cctgaggtca gcgtgcgtct ttgtcaccag tgggcactgg
 601 agtgtgaaga gctgagcagt ccctatgatg tccagaaaat tgtgtctggg ggccacactg
 661 tagagctgcc ttatgaattc cttctgccct gtctgtgcat agaggcatcc tacctgcaag
 721 aggacactgt gaggcgcaaa aaatgtccct tccagagctg gccagaagcc tatggctcgg
 781 acttctggaa gtcagtgcac ttcactgact acagccagca cactcagatg gtcatggccc
 841 tgacactccg ctgcccactg aagctggaag ctgccctctg ccagaggcac gactggcata
 901 ccctttgcaa agacctcccg aatgccacag ctcgagagtc agatgggtgg tatgttttgg
 961 agaaggtgga cctgcacccc cagctctgct tcaagttctc ttttggaaac agcagccatg
1021 ttgaatgccc ccaccagact gggtctctca catcctggaa tgtaagcatg gatacccaag
1081 cccagcagct gattcttcac ttctcctcaa gaatgcatgc caccttcagt gctgcctgga
1141 gcctcccagg cttggggcag gacactttgg tgccccccgt gtacactgtc agccaggccc
1201 ggggctcaag cccagtgtca ctagacctca tcattccctt cctgaggcca gggtgctgtg
1261 tcctggtgtg gcggtcagat gtccagtttg cctggaagca cctcttgtgt ccggatgtct
1321 cttacagaca cctggggctc ttgatcctgg cactgctggc cctcctcacc ctactgggtg
1381 ttgttctggc cctcacctgc cggcgcccac agtcaggccc gggcccagcg cggccagtgc
1441 tcctcctgca cgcggcggac tcggaggcgc agcggcgcct ggtgggagcg ctggctgaac
1501 tgctacgggc agcgctgggc ggcgggcgcg acgtgatcgt ggacctgtgg gaggggaggc
1561 acgtggcgcg cgtgggcccg ctgccgtggc tctgggcggc gcggacgcgc gtagcgcggg
1621 agcagggcac tgtgctgctg ctgtggagcg gcgccgacct tcgcccggtc agcggccccg
1681 acccccgcgc cgcgcccctg ctcgccctgc tccacgctgc cccgcgcccg ctgctgctgc
1741 tcgcttactt cagtcgcctc tgcgccaagg gcgacatccc cccgccgctg cgcgccctgc
1801 cgcgctaccg cctgctgcgc gacctgccgc gtctgctgcg ggcgctggac gcgcggcctt
1861 tcgcagaggc caccagctgg ggccgccttg gggcgcggca gcgcaggcag agccgcctag
1921 agctgtgcag ccggctcgaa cgagaggccg cccgacttgc agacctaggt tgagcagagc
1981 tccaccgcag tcccgggtgt ctgcggccgc aacgcaacgg acactggctg gaaccccgga
2041 atgagccttc gaccctgaaa tccttggggt gcctcgagga cgactggccg aaaagccgca
2101 ttccctgcct cacaggccgg aagtcccagc ccagtccccg cgcgcgtccc tcttcctcct
2161 catactttcc cttgactgag agctcctcta acccctgttc tgatggggga gggcggtctt
2221 cccacttcct ctccagaact ccagaaagag cagtgtgctt atgcttcagt ccaggctgga
2281 gaggttgggg ccggggtagg gaggcaggag ccatgtcagt tctgaaggag ggtgaggcgg
2341 tgggggattg caggggcgg ctgagagaaa acctccttgg gggccaggga ttccctttcc
2401 cactctgagg ctctggccag agggagagag gactctggac ctaggaaaag aggcttttgg
2461 ctccaggtgg tcaggacagt gggggttggg ggtggggtgg gtgggtgctg gcggtgggga
2521 ccaagatccg gaaagatgaa taaagacaaa catgacaaac taagaaaaaa aaaaaaaaaa
2581 a
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[136] IL-17RE, transcript variant 2, is encoded by the following amino acid sequence (NCBI Accession No. NM_153481 and SEQ ID NO: 30):

MPAPAQRKLLPRRHLSEKSHHISIPSPDISHKGLRSKRTQPSDPETWESLPRLDSQRHGGPEFSFDLLPEA
RAIRVTISSGPEVSVRLCHQWALECEELSSPYDVQKIVSGGHTVELPYEFLLPCLCIEASYLQEDTVRRK
KCPFQSWPEAYGSDFWKSVHFTDYSQHTQMVMALTLRCPLKLEAALCQRHDWHTLCKDLPNATARE
SDGWYVLEKVDLHPQLCFKFSFGNSSHVECPHQTGSLTSWNVSMDTQAQQLILHFSSRMHATFSAAW
SLPGLGQDTLVPPVYTVSQARGSSPVSLDLIIPFLRPGCCVLVWRSDVQFAWKHLLCPDVSYRHLGLLIL
ALLALLTLLGVVLALTCRRPQSGPGPARPVLLLHAADSEAQRRLVGALAELLRAALGGGRDVIVDLWE
GRHVARVGPLPWLWAARTRVAREQGTVLLLWSGADLRPVSGPDPRAAPLLALLHAAPRPLLLLAYFS
RLCAKGDIPPPLRALPRYRLLRDLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLEREAARLA
DLG

[137] IL-17RE, transcript variant 5, is encoded by the following mRNA sequence (NCBI Accession No. NM_153483 and SEQ ID NO: 31):

```
   1 ggtgcgtccc ccaacctgat gctagcccct ttcctgttac ttctcaccca cagcaggagc
  61 cccttgtctt tcaggccatg cagccatgtt ccgggagccc taattgcaca gaagcccATG
 121 gggagctcca gactggcagc cctgctcctg cctctcctcc tcatagtcat cgacctctct
 181 gactctgctg ggattggctt tcgccacctg ccccactgga acacccgctg tcctctggcc
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 241 tcccacacgg atgacagttt cactggaagt tctgcctata tcccttgccg cacctggtgg
 301 gccctcttct ccacaaagcc ttggtgtgtg cgagtctggc actgttcccg ctgtttgtgc
 361 cagcatctgc tgtcaggtgg ctcaggtctt caacggggcc tcttccacct cctggtgcag
 421 aaatccaaaa agtcttccac attcaagttc tataggagac acaagatgcc agcacctgct
 481 cagaggaagc tgctgcctcg tcgtcacctg tctgagaaga gccatcacat ttccatcccc
 541 tccccagaca tctcccacaa gggacttcgc tctaaaagga cccaaccttc ggatccagag
 601 acatgggaaa gtcttcccag attggactca caaaggcatg gaggacccga gttctccttt
 661 gatttgctgc ctgaggcccg ggctattcgg gtgaccatat cttcaggccc tgaggtcagc
 721 gtgcgtcttt gtcaccagtg ggcactggag tgtgaagagc tgagcagtcc ctatgatgtc
 781 cagaaaattg tgtctggggg ccacactgta gagctgcctt atgaattcct tctgccctgt
 841 ctgtgcatag aggcatccta cctgcaagag gacactgtga ggcgcaaaaa atgtcccttc
 901 cagagctggc cagaagccta tggctcggac ttctggaagt cagtgcactt cactgactac
 961 agccagcaca ctcagatggt catggccctg acactccgct gcccactgaa gctggaagct
1021 gccctctgcc agaggcacga ctggcatacc ctttgcaaag acctcccgaa tgccacagct
1081 cgagagtcag atgggtggta tgttttggag aaggtggacc tgcaccccca gctctgcttc
1141 aagttctctt ttggaaacag cagccatgtt gaatgccccc accagactgg gtctctcaca
1201 tcctggaatg taagcatgga tacccaagcc cagcagctga ttcttcactt ctcctcaaga
1261 atgcatgcca ccttcagtgc tgcctggagc ctcccaggct tggggcagga cactttggtg
1321 ccccccgtgt acactgtcag ccaggcccgg ggctcaagcc cagtgtcact agacctcatc
1381 attcccttcc tgaggccagg gtgctgtgtc ctggtgtggc ggtcagatgt ccagtttgcc
1441 tggaagcacc tcttgtgtcc ggatgtctct tacagacacc tggggctctt gatcctggca
1501 ctgctggccc tcctcaccct actgggtgtt gttctggccc tcacctgccg gcgcccacag
1561 tcaggcccgg gcccagcgcg gccagtgctc ctcctgcacg cggcggactc ggaggcgcag
1621 cggcgcctgg tgggagcgct ggctgaactg ctacgggcag cgctgggcgg cgggcgcgac
1681 gtgatcgtgg acctgtggga ggggaggcac gtggcgcgcg tgggcccgct gccgtggctc
1741 tgggcggcgc ggacgcgcgt agcgcgggag cagggcactg tgctgctgct gtggagcggc
1801 gccgaccttc gcccggtcag cggccccgac ccccgcgccg cgcccctgct cgccctgctc
1861 cacgctgccc cgcgcccgct gctgctgctc gcttacttca gtcgcctctg cgccaagggc
1921 gacatccccc cgccgctgcg cgccctgccg cgctaccgcc tgctgcgcga cctgccgcgt
1981 ctgctgcggg cgctggacgc gcggcctttc gcagaggcca ccagctgggg ccgccttggg
2041 gcgcggcagc gcaggcagag ccgcctagag ctgtgcagcc ggctcgaacg agaggccgcc
2101 cgacttgcag acctaggttg agcagagctc caccgcagtc ccgggtgtct gcggccgcaa
2161 cgcaacggac actggctgga accccggaat gagccttcga ccctgaaatc cttggggtgc
2221 ctcgaggacg actggccgaa aagccgcatt ccctgcctca caggccggaa gtcccagccc
2281 agtccccgcg cgcgtccctc ttcctcctca tactttccct tgactgagag ctcctctaac
2341 ccctgttctg atgggggagg gcggtcttcc cacttcctct ccagaactcc agaaagagca
2401 gtgtgcttat gcttcagtcc aggctggaga ggttggggcc ggggtaggga ggcaggagcc
2461 atgtcagttc tgaaggaggg tgaggcggtg ggggattgca gggggcggct gagagaaaac
2521 ctccttgggg gccagggatt ccctttccca ctctgaggct ctggccagag ggagagagga
2581 ctctggacct aggaaaagag gcttttggct ccaggtggtc aggacagtgg gggttggggg
2641 tggggtgggt gggtgctggc ggtggggacc aagatccgga aagatgaata aagacaaaca
2701 tgacaaacta agaaaaaaaa aaaaaaaaa
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[138] IL-17RE, transcript variant 5, is encoded by the following amino acid sequence (NCBI Accession No. NM_153483 and SEQ ID NO: 32):

```
MGSSRLAALLLPLLLIVIDLSDSAGIGFRHLPHWNTRCPLASHTDDSFTGSSAYIPCRTWWALFSTKPWC
VRVWHCSRCLCQHLLSGGSGLQRGLFHLLVQKSKKSSTFKFYRRHKMPAPAQRKLLPRRHLSEKSHHI
SIPSPDISHKGLRSKRTQPSDPETWESLPRLDSQRHGGPEFSFDLLPEARAIRVTISSGPEVSVRLCHQWA
LECEELSSPYDVQKIVSGGHTVELPYEFLLPCLCIEASYLQEDTVRRKKCPFQSWPEAYGSDFWKSVHF
TDYSQHTQMVMALTLRCPLKLEAALCQRHDWHTLCKDLPNATARESDGWYVLEKVDLHPQLCFKFS
FGNSSHVECPHQTGSLTSWNVSMDTQAQQLILHFSSRMHATFSAAWSLPGLGQDTLVPPVYTVSQARG
SSPVSLDLIIPFLRPGCCVLVWRSDVQFAWKHLLCPDVSYRHLGLLILALLALLTLLGVVLALTCRRPQS
GPGPARPVLLLHAADSEAQRRLVGALAELLRAALGGGRDVIVDLWEGRHVARVGPLPWLWAARTRV
AREQGTVLLLWSGADLRPVSGPDPRAAPLLALLHAAPRPLLLLAYFSRLCAKGDIPPPLRALPRYRLLR
DLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLEREAARLADLG
```

Silencing Expression with MicroRNAs

[139] The invention comprises compositions with means to inhibit the activity of IL-17 or an IL-17R, by delivering microRNA (miRNA) molecules to an ocular or adnexal tissue with an appropriate pharmaceutical carrier. Compositions that comprise a miRNA targeted to either IL-17 or an IL-17R antagonize the function of an IL-17R. The composition comprises one or more miRNA(s) that bind to one or more regions of IL-17 or an IL-17R. The following table contains exemplary miRNAs that have been shown to partially or completely silence the expression of human IL-17 or an IL-17R.

Table 1: Summary of miRNAs, their human target genes, nucleotide sequences, and their sequence identifier numbers.

Target Gene	miRNA	Polynucleotide sequence (5' to 3')	SEQ ID NO:
IL-17R	miR-24	UGGCUCAGUUCGGAACAG	33
IL-17R	miR-378	CUCCUGACUCCAGGUCCUGUGU	34
IL-17R	Let-7g	UGAGGUAGUAGUUUGUACAGU	35

Pharmaceutically-Appropriate Carriers

[140] Exemplary compounds incorporated to facilitate and expedite transdermal delivery of topical compositions into ocular or adnexal tissues include, but are not limited to, alcohol (ethanol, propanol, and nonanol), fatty alcohol (lauryl alcohol), fatty acid (valeric acid, caproic acid and capric acid), fatty acid ester (isopropyl myristate and isopropyl n-hexanoate), alkyl ester (ethyl acetate and butyl acetate), polyol (propylene glycol, propanedione and hexanetriol), sulfoxide (dimethylsulfoxide and decylmethylsulfoxide), amide (urea, dimethylacetamide and pyrrolidone derivatives), surfactant (sodium lauryl sulfate, cetyltrimethylammonium bromide, polaxamers, spans, tweens, bile salts and lecithin), terpene (d-limonene, alpha-terpeneol, 1,8-cineole and menthone), and alkanone (N-heptane and N-nonane). Moreover, topically-administered compositions comprise surface adhesion molecule modulating agents including, but not limited to, a cadherin antagonist, a selectin antagonist, and an integrin antagonist.

[141] Optionally, the composition further contains a compound selected from the group consisting of a physiological acceptable salt, poloxamer analogs with carbopol, carbopol/hydroxypropyl methyl cellulose (HPMC), carbopol-methyl cellulose, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

Drug Delivery by Contact Lens

[142] The invention comprises a contact lens and a composition that inhibits an activity of an inflammatory interleukin-1 cytokine. For example, the composition is incorporated into or coated onto said lens. The composition is chemically bound or physically entrapped by the contact lens polymer. Alternatively, a color additive is chemically bound or physically entrapped by the polymer composition that is released at the same rate as the therapeutic drug composition, such that changes in the intensity of the color additive indicate changes in the amount or dose of therapeutic drug composition remaining bound or entrapped within the polymer. Alternatively, or in addition, an ultraviolet (UV) absorber is chemically bound or physically entrapped within the contact lens polymer. The contact lens is either hydrophobic or hydrophilic.

[143] Exemplary materials used to fabricate a hydrophobic lens with means to deliver the compositions of the invention include, but are not limited to, amefocon A, amsilfocon A, aquilafocon A, arfocon A, cabufocon A, cabufocon B, carbosilfocon A, crilfocon A, crilfocon B, dimefocon A, enflufocon A, enflofocon B, erifocon A, flurofocon A, flusilfocon A, flusilfocon B, flusilfocon C, flusilfocon D, flusilfocon E, hexafocon A, hofocon A, hybufocon A, itabisfluorofocon A, itafluorofocon A, itafocon A, itafocon B, kolfocon A, kolfocon B, kolfocon C, kolfocon D, lotifocon A, lotifocon B, lotifocon C, melafocon A, migafocon A, nefocon A, nefocon B, nefocon C, onsifocon A, oprifocon A, oxyfluflocon A, paflufocon B, paflufocon C, paflufocon D, paflufocon E, paflufocon F, pasifocon A, pasifocon B, pasifocon C, pasifocon D, pasifocon E, pemufocon A, porofocon A, porofocon B, roflufocon A, roflufocon B, roflufocon C, roflufocon D, roflufocon E, rosilfocon A, satafocon A, siflufocon A, silafocon A, sterafocon A, sulfocon A, sulfocon B, telafocon A, tisilfocon A, tolofocon A, trifocon A, unifocon A, vinafocon A, and wilofocon A.

[144] Exemplary materials used to fabricate a hydrophilic lens with means to deliver the compositions of the invention include, but are not limited to, abafilcon A, acofilcon A, acofilcon B, acquafilcon A, alofilcon A, alphafilcon A, amfilcon A, astifilcon A, atlafilcon A, balafilcon A, bisfilcon A, bufilcon A, comfilcon A, crofilcon A, cyclofilcon A, darfilcon A, deltafilcon A, deltafilcon B, dimefilcon A, droxfilcon A, elastofilcon A, epsilfilcon A, esterifilcon A, etafilcon A, focofilcon A, galyfilcon A, genfilcon A, govafilcon A, hefilcon A, hefilcon B, hefilcon C, hilafilcon A, hilafilcon B, hioxifilcon A, hioxifilcon B, hioxifilcon C, hydrofilcon A, lenefilcon A, licryfilcon A, licryfilcon B, lidofilcon A, lidofilcon B, lotrafilcon A, lotrafilcon B, mafilcon A, mesafilcon A, methafilcon B, mipafilcon A, nelfilcon A, netrafilcon A, ocufilcon A, ocufilcon B, C, ocufilcon D, ocufilcon E, ofilcon A,

omafilcon A, oxyfilcon A, pentafilcon A, perfilcon A, pevafilcon A, phemfilcon A, polymacon, senofilcon A, silafilcon A, siloxyfilcon A, surfilcon A, tefilcon A, tetrafilcon A, trilfilcon A, vifilcon A, vifilcon B, and xylofilcon A.

Antibody Compositions:

[145] Compositions of the claimed invention comprise at least one antibody. This antibody is either monoclonal or polyclonal. The claimed antibody targets an intracellular or extracellular IL-17 cytokine or IL-17 receptor, preferably, the IL-17A or F cytokine or the IL-17RA or IL-17RC receptor. This antibody binds to at least one intracellular or extracellular sequence, or epitope, of an IL-17 cytokine or IL-17 receptor. In certain embodiments, the claimed antibody is a single-chain antibody. Alternatively, the antibody is a humanized, recombinant, or chimeric antibody. This antibody is optionally derived from commercially-available antibodies designed for in vitro or in vivo use. The claimed antibody is conjugated directly or indirectly to one or more compound(s) that inhibit or modify the activity of an IL-17 cytokine or an IL-17 receptor. Alternatively, the claimed antibody is an intracellular antibody, or intrabody.

[146] The claimed antibody binds to one or more regions of an IL-17 cytokine. Exemplary regions to which the claimed antibody binds include, but are not limited to, an intracellular domain, an extracellular domain, a catalytic domain, a protein-binding domain, a ligand-binding domain, a scaffolding domain, a signal peptide, a domain of an immature cytokine, a precursor domain, a fibronectin domain, a linker region, a regulatory domain, an oligomerization domain, or a signaling domain.

EXAMPLES

EXAMPLE 1: $CD4^+IL\text{-}17^+$ T Cell Abundance in a Mouse Model of DES

[147] Dry Eye Syndrome (DES) was induced in mice by subcutaneous injection of scopolamine and placement in controlled-environment chambers. Following induction of DES and an incubation period, the abundance of $CD4^+IL\text{-}17^+$ T cells in draining lymph nodes was measured using flow cytometry. For Examples 1-4, the monoclonal anti-mouse IL-17 antibody used was obtained from R&D Systems, Inc. (Clone: 50104, Cat. # MAB421). Figure 1 shows that the abundance of IL-17-producing $CD4^+$ T cells in the draining lymph nodes of mice with DES increases compared to those of healthy controls.

EXAMPLE 2: IL-17 mRNA Expression in Conjunctiva of DES Mice

[148] IL-17 mRNA transcripts expressed within the conjunctiva of DES versus normal mice was quantified using real time polymerase chain reaction (PCR). The conjunctiva is the thin,

transparent tissue that covers the outer surface of the eye. This structure begins at the outer edge of the cornea, covering the visible part of the sclera, and lining the inside of the eyelids. DES mice demonstrated a three fold increase in the abundance of IL-17 mRNA transcripts in this structure compared to healthy controls, as shown in Figure 2.

EXAMPLE 3: IL-17RA Expression on Ocular Surfaces

[149] IL-17 receptor expression on ocular surfaces was analyzed using immuno-fluorescence microscopy. In contrast to the dramatic upregulation of IL-17 mRNA in the conjunctiva of DES mice, Figure 3 shows that IL-17RA protein was constitutively expressed on corneal as well as conjunctival epithelium of both DES and control groups.

EXAMPLE 4: *In Vivo* Blockade of IL-17 in DES Mice

[150] Healthy and DES mice were intraperitoneally injected with neutralizing anti-IL-17 antibodies to determine the effect of blocking IL-17 activity on both the induction and progression of DES. The results showed a significant decrease in the intensity of clinical signs of DES (measured by corneal fluorescein staining (CFS) scoring) during the induction as well as the progression phases of the disease in the anti-IL-17 antibody-treated group as compared to the control antibody-treated group (shown in Figure 4, panels a and b). Furthermore, lymph nodes and conjunctiva of the anti-IL-17 antibody-treated group showed reductions in the abundance of Th17 cells and the expression of IL-17 mRNA, respectively, compared to the control-antibody treated group (shown in Figure 4, panels c and d).

[151] Figure 5 shows the oxford schema for grading corneal and conjunctival staining used for scoring clinical severity in this example.

EXAMPLE 5: Recovery of regulatory T-cell (Treg) suppressor function by anti-IL-17 therapy.

[152] The *in vitro* Treg suppression assay using CD3 stimulated primed-T cells (isolated from the LN of dry eye mice) and Tregs (isolated from the LN of mice treated with anti-IL-17 or isotype antibodies) shows a significant recovery in the suppressor potential of Tregs only in mice treated with anti-IL-17 antibody (i.p.) compared to those isolated from the isotype antibody treated groups ($p = 0.029$). The suppressor potential of Tregs isolated from different groups is calculated in relation to the suppression potential of Tregs of normal mice, considered as 100% (Figure 7).

[153] In dry eye disease there is a significant functional loss of Treg suppression of about 50%. Anti-IL-17 antibody treatment promotes Treg function and restores and/or augments Treg-mediated immune suppression.

EXAMPLE 6: Topical application of anti-IL-17 antibody ameliorates Dry Eye Disease

[154] Figure 8A shows a schematic diagram of the experimental design to study the effects of *in vivo* IL-17 blockade using topical application of anti-IL17-antibody or isotype-antibody on clinical signs. CFS are significantly lower in anti-IL-17 antibody-treated mice compared to isotype antibody-treated and untreated groups (Figures 8B and 8C).

EXAMPLE 7: Topical application of anti-IL-17 antibody reduces frequencies of pathogenic Th17 cells both in conjunctiva and the draining lymph nodes.

[155] Conjunctiva and the draining lymph nodes were harvested at Day 10 (as shown in Fig 8) from Anti-IL17 antibody and Isotype antibody treated mice. Real-time PCR was performed to analyze mRNA expression levels of IL-17 (Th17 cells) and Foxp3 (Treg cells). Figures 9A and 9B show that treatment with an anti-IL-17 antibody specifically decreases expression of IL-17 in Th17 cells of the conjunctiva and lymph nodes.

EXAMPLE 8: Topical application of anti-IL-17 antibody inhibits dry eye induced corneal lymphatic vessels via decreased secretion of lymphangiogenesis-specific growth factors, particularly VEGF-C and D in dry eye corneas.

[156] Induction of new lymphatic vessels in dry eye corneas facilitate the migration of resident corneal antigen presenting cells to the draining lymph nodes, which, in turn, induce generation of adaptive immunity to ocular surface. Untreated and control Ab treated Dry Eye groups show an invasion of lymphatic vessels into the cornea (Figure 10A), compared to Normal cornea. Treatment with anti-IL-17 antibody decreases invasion of lymphatic vessels into the cornea (Figure 10A). Anti-IL17 antibody treatment decreases mRNA expression of known angiogenic molecules, such as VEGF-C, VEGF-D, and VEGFR-3 (Figure 10B).

EXAMPLE 9: Topical application of anti-IL-17 antibody maintains the normal phenotype of CD11b+ cells in cornea.

[157] Corneas of Anti-IL-17antibody-treated group show that similar to normal cornea, majority of CD11b+ cells have phenotype of resident dendritic cells. However, corneas of isotype-antibody treated group show that the phenotype of majority of CD11b+ cells are similar to the infiltrating pathogenic macrophages/monocytes (Figure 11).

EXAMPLE 10: Topical application of anti-IL-17 antibody prevents corneal nerve degeneration.

[158] Figure 12 shows representative micrographs of corneal whole mount depicting epithelial and sub-epithelial nerves (Tubulin-III, Red) in different groups. Patterns of nerves

in the corneas of Anti-IL17-antibody treated group show similarity to those in the normal corneas, whereas corneas of isotype-antibody treated group show loss of epithelial nerves.

EXAMPLE 11: Human Corneal Epithelial Cells Respond to IL-17 Cytokine by Increased Secretion of Lymphangiogenesis-Specific Growth Factors.

[159] To delineate the mechanism(s) of IL-17 mediated lymphangiogenesis in the corneas of dry eye mice (as shown in Fig. 4) and to ensure that IL-17 has similar effects on human cornea, primary human corneal epithelial cells were cultured for 24h in the presence of IL-17 and the gene expression levels of different VEGF-species were compared to normal untreated cells (Figure 14A). Real time PCR analyses show that IL-17 treated human corneal epithelial cells express higher levels of lymphangiogenesis-specific growth factors, particularly VEGF-D (4-fold) and VEGF-C (1.8-fold) compared to untreated cells (Figure 14B).

EXAMPLE 12: Topical application of anti-IL-17 antibody enhances corneal nerve regeneration.

[160] Anti-IL-17 antibody treatment is applied to the isotype-antibody treated group of Example 10 or non-treated group of mice. Corneas are treated as described above for Example 10. Anti-IL-17 antibody treatment enhances nerve regeneration such that the amount of nerve fibers associated with damaged corneas is increased compared to untreated or isotype-treated corneas.

OTHER EMBODIMENTS

[161] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

[162] Deleted.

[163] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Use of a composition that inhibits binding of an inflammatory interleukin-17 (IL-17) cytokine to an IL-17 receptor to reduce the severity of Dry Eye Syndrome, wherein the composition is formulated for local, topical administration to an eye of a subject in need thereof, wherein said composition comprises an antibody or antigen-binding fragment thereof targeted against said inflammatory IL-17 cytokine or the IL-17 receptor, an intrabody that binds to an IL-17 receptor complex or a soluble fragment of the IL-17 receptor complex which binds IL-17.

2. Use of a composition that inhibits binding of an inflammatory interleukin-17 (IL-17) cytokine to an IL-17 receptor in the manufacture of a medicament to reduce the severity of Dry Eye Syndrome, wherein the composition is formulated for local administration to an eye of a subject in need thereof wherein said composition comprises an antibody or antigen-binding fragment thereof targeted against the inflammatory IL-17 cytokine or the IL-17 receptor, an intrabody that binds to an IL-17 receptor complex or a soluble fragment of the IL-17 receptor complex which binds IL-17.

3. The use of claim 1 or 2, wherein said subject exhibits a sign or symptom selected from the group consisting of eye dryness, scratching, stinging, itching, burning, irritation, pain, redness, inflammation, discharge, and excessive watering, and wherein said composition inhibits or reduces the severity of at least one of said signs or symptoms.

4. The use of claim 1 or 2, wherein said Dry Eye Syndrome comprises keratoconjunctivitis sicca (KCS), Sjögren syndrome (SS), Sjögren syndrome associated keratoconjunctivitis sicca, non-Sjögren syndrome associated keratoconjunctivitis sicca, keratitis sicca, sicca syndrome, xerophthalmia, tear film disorder, decreased tear production, aqueous tear deficiency (ATD), meibomian gland dysfunction, or evaporative loss.

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5. The use of claim 1 or 2, wherein the composition that inhibits binding of an inflammatory IL-17 cytokine to an IL-17 receptor is for sequential or simultaneous administration along with a secondary composition.

6. The use of claim 1 or 2, wherein the composition is formulated as a solid, an ointment, a gel, a liquid, an aerosol, a mist, a polymer, a contact lens, a film, an emulsion, or a suspension.

7. The use of claim 1, wherein said composition is incorporated into or coated onto a contact lens.

8. The use of claim 2, wherein said composition is for topical administration.

9. The use of claim 1 or 2, wherein said use does not comprise systemic administration or substantial dissemination to non-ocular tissue.

10. The use of claim 1 or 2, wherein said composition further comprises a compound selected from the group consisting of a physiological acceptable salt, poleaxes analogs with carbopol, carbopol/ hydroxypropyl methyl cellulose (HPMC), carbopol-methyl cellulose, a mucolytic agent, carboxymethylcellulose (CMC), hyaluronic acid, cyclodextrin, and petroleum.

11. The use of claim 1, wherein said composition that inhibits binding of an inflammatory IL-17 cytokine to an IL-17 receptor is for administration with a second composition comprising one or more inflammatory antagonist(s).

12. The use according to claim 11, wherein said second composition comprises cyclosporin A at a concentration of 0.05 - 4.0 mg/ml, a glucocorticoid, a cytostatic agent, an alkylating agent, an antimetabolic agent, a cytotoxic antibiotic, Atgam polyclonal antibody, Atgam and Thympglobuline polyclonal antibody, any antibody against the antilymphocyte or antithymocyte antigens, a OKT3 monoclonal antibody, any antibody against the T-cell receptor, any antibody against IL-2, basiliximab, declizumab, Tacrolimus/FK506, Sirolimus/Rapamycin, interferon beta, interferon gamma, an opioid, a TNFα binding protein, mycophenolate, or FTY720.

Date Reçue/Date Received 2020-10-14

13. The use of claim 1 or 2, wherein said antibody is:

(a) a monoclonal or polyclonal antibody;

(b) an antibody that targets an intracellular or extracellular IL-17 cytokine or IL-17 receptor;

(c) an antibody that binds to at least one intracellular or extracellular domain of an IL-17 cytokine or IL-17 receptor;

(d) a single-chain antibody;

(e) a humanized, recombinant, or chimeric antibody; or

(f) an antibody conjugated directly or indirectly to a small molecule that inhibits or modifies the binding of an IL-17 cytokine or an IL-17 receptor.

14. The use of claim 1 or 2, wherein said cytokine is selected from the group consisting of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F.

15. The use of any one of claims 1 or 2, wherein said IL-17 receptor is selected from the group consisting of IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE.

16. The use of claim 10, wherein said mucolytic agent is N-acetyl cysteine.

17. The use of any one of claims 1 to 16, wherein said Dry Eye Syndrome is caused by a transplant.

18. The use of claim 17, wherein said transplant is bone marrow transplant.

19. The use of any one of claims 1 to 16, wherein said Dry Eye Syndrome is caused by corneal transplant.

20. The use of claim 19, wherein said corneal transplant comprises keratoprosthesis.

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21. Use of a composition that inhibits binding of an inflammatory interleukin-17 (IL-17) cytokine to an IL-17 receptor in the manufacture of a medicament to reduce the severity of Dry Eye Syndrome, wherein the medicament is formulated for local, topical administration to an eye of a subject in need thereof, wherein said composition comprises an antibody or antigen-binding fragment thereof targeted against the inflammatory IL-17 cytokine or the IL-17 receptor, an intrabody that binds to an IL-17 receptor complex or a soluble fragment of the IL-17 receptor complex which binds IL-17.

Date Reçue/Date Received 2020-10-14

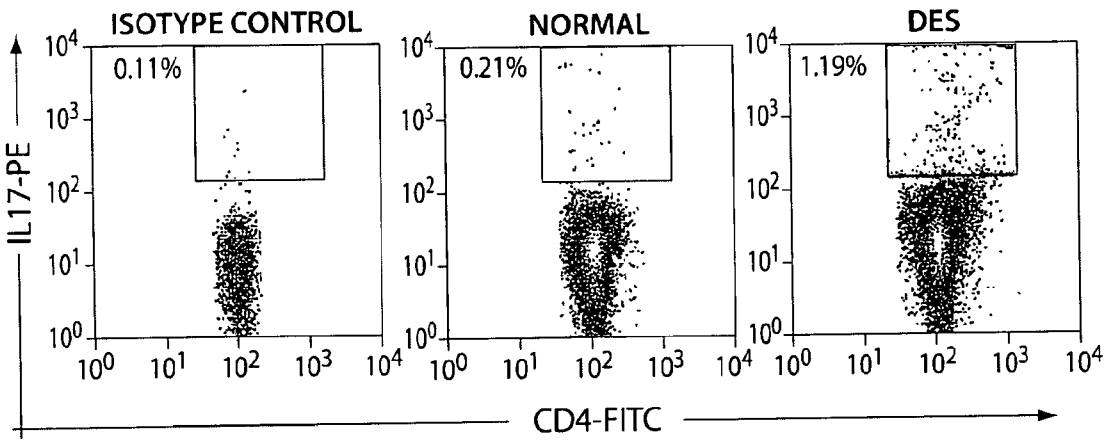

ISOTYPE CONTROL
NORMAL
DES
0.11%
0.21%
1.19%
IL17-PE
CD4-FITC
10^0 10^1 10^2 10^3 10^4

Fig. 1

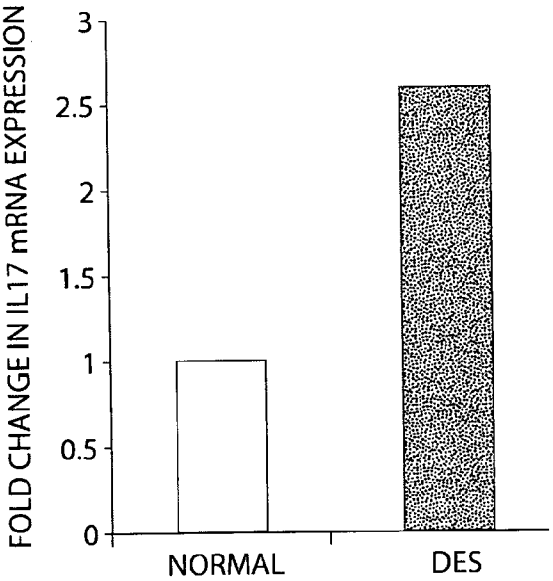


Fig. 2

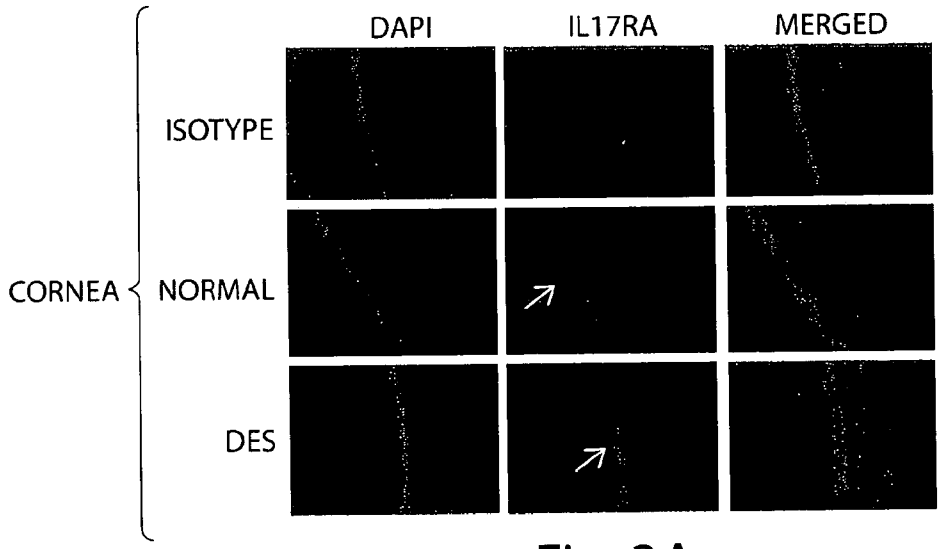

DAPI
IL17RA
MERGED
ISOTYPE
CORNEA
NORMAL
DES

Fig. 3A

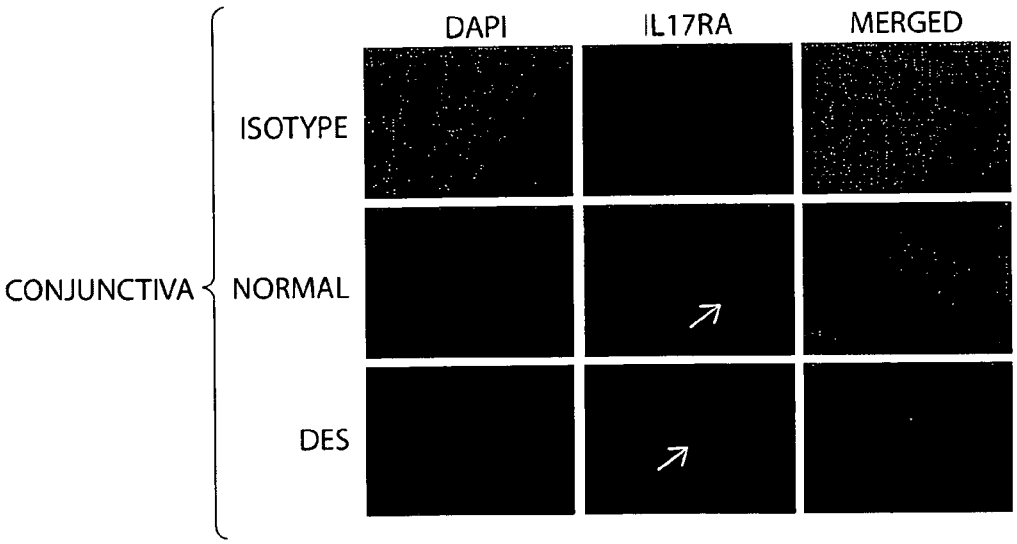

DAPI
IL17RA
MERGED
ISOTYPE
CONJUNCTIVA
NORMAL
DES

Fig. 3B

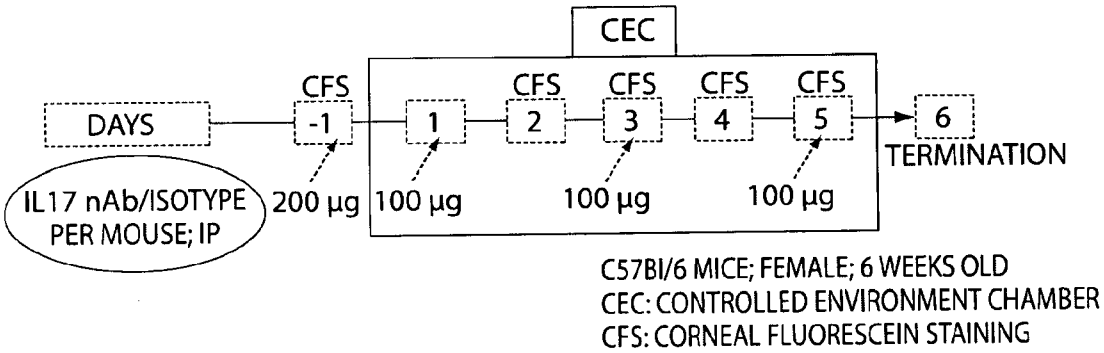

CEC
CFS
CFS
CFS
CFS
CFS
DAYS
-1
1
2
3
4
5
6
TERMINATION
IL17 nAb/ISOTYPE PER MOUSE; IP
200 µg
100 µg
100 µg
100 µg
C57Bl/6 MICE; FEMALE; 6 WEEKS OLD
CEC: CONTROLLED ENVIRONMENT CHAMBER
CFS: CORNEAL FLUORESCEIN STAINING

Fig. 4A

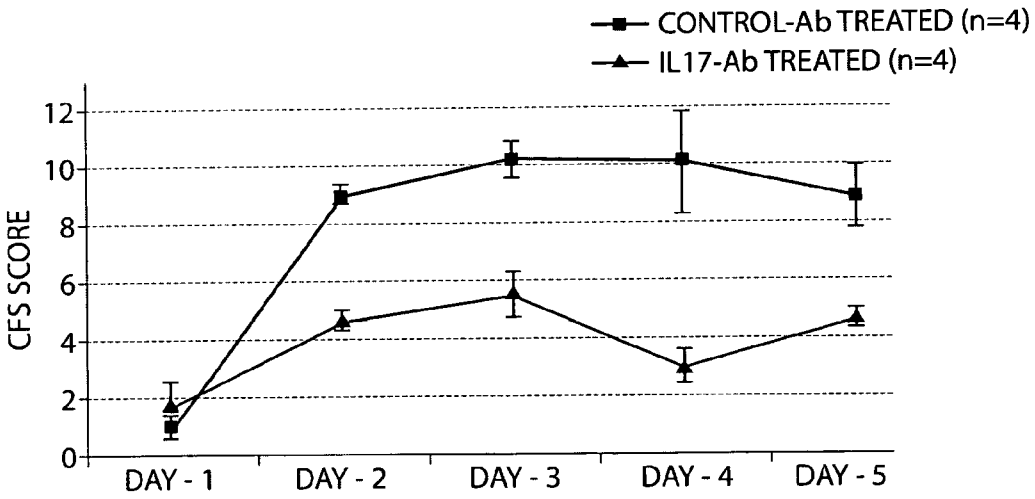

CONTROL-Ab TREATED (n=4)
IL17-Ab TREATED (n=4)
CFS SCORE
0
2
4
6
8
10
12
DAY - 1
DAY - 2
DAY - 3
DAY - 4
DAY - 5

Fig. 4B

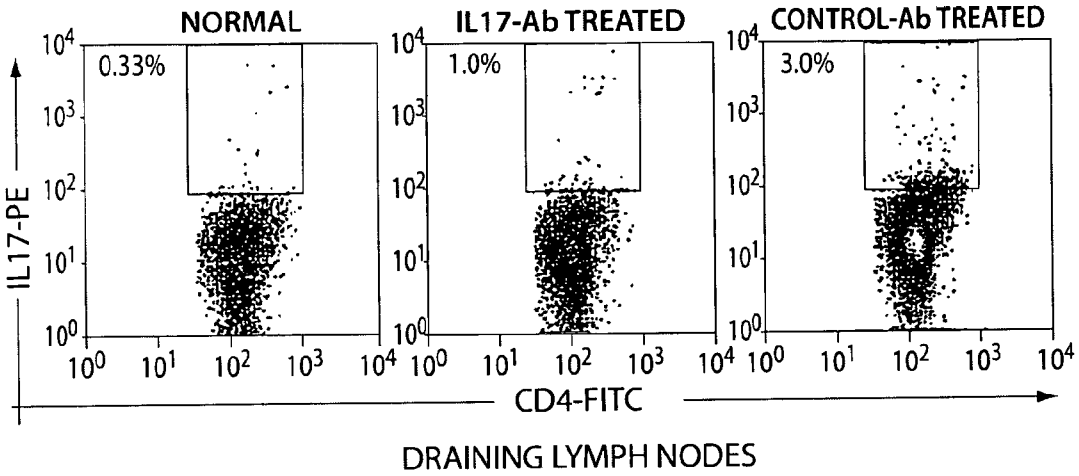

NORMAL
IL17-Ab TREATED
CONTROL-Ab TREATED
0.33%
1.0%
3.0%
IL17-PE
CD4-FITC
DRAINING LYMPH NODES

Fig. 4C

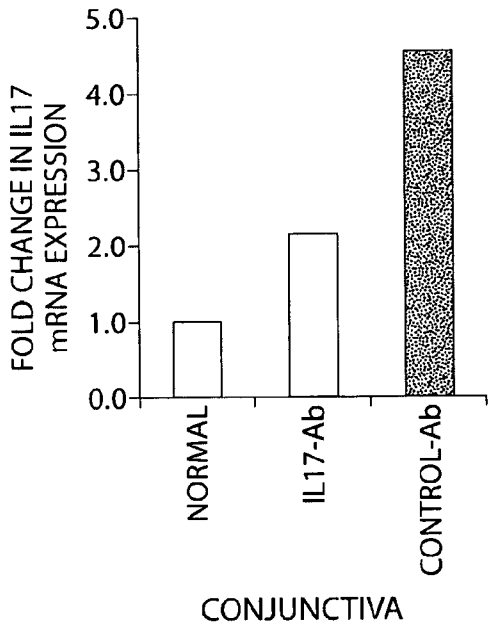

FOLD CHANGE IN IL17 mRNA EXPRESSION
5.0
4.0
3.0
2.0
1.0
0.0
NORMAL
IL17-Ab
CONTROL-Ab
CONJUNCTIVA

Fig. 4D

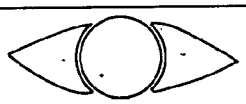
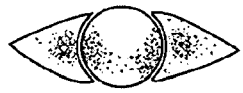
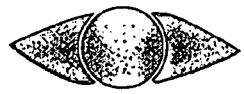
PANEL	GRADE	CRITERIA
A 	0	EQUAL TO OR LESS THAN PANEL A
B 	I	EQUAL TO OR LESS THAN PANEL B, GREATER THAN A
C 	II	EQUAL TO OR LESS THAN PANEL C, GREATER THAN B
D 	III	EQUAL TO OR LESS THAN PANEL D, GREATER THAN C
E 	IV	EQUAL TO OR LESS THAN PANEL E, GREATER THAN D
>E	V	GREATER THAN PANEL E

Fig. 5

Ocular Surface Disease Index (OSDI)

Circle the number in the box that best represents each answer.

Have you experienced any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Have problems with your eyes limited you in performing any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6.Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Have your eyes felt uncomfortable in any of the following situations during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Total score for answers 1 to 12 _____

Total number of questions answered _____
(Do not include questions answered N/A)

OSDI = (sum of scores)/(# of questions answered) _____

Fig. 6

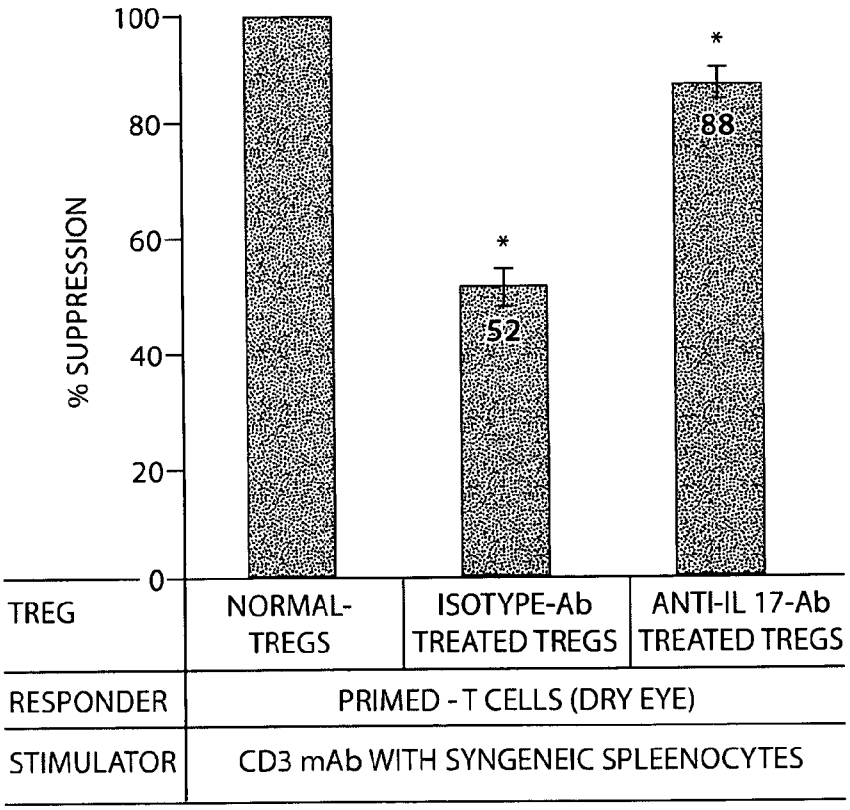

100
80
60
40
20
0
% SUPPRESSION
*
52
*
88
TREG
NORMAL-TREGS
ISOTYPE-Ab TREATED TREGS
ANTI-IL 17-Ab TREATED TREGS
RESPONDER
PRIMED - T CELLS (DRY EYE)
STIMULATOR
CD3 mAb WITH SYNGENEIC SPLEENOCYTES

Fig. 7

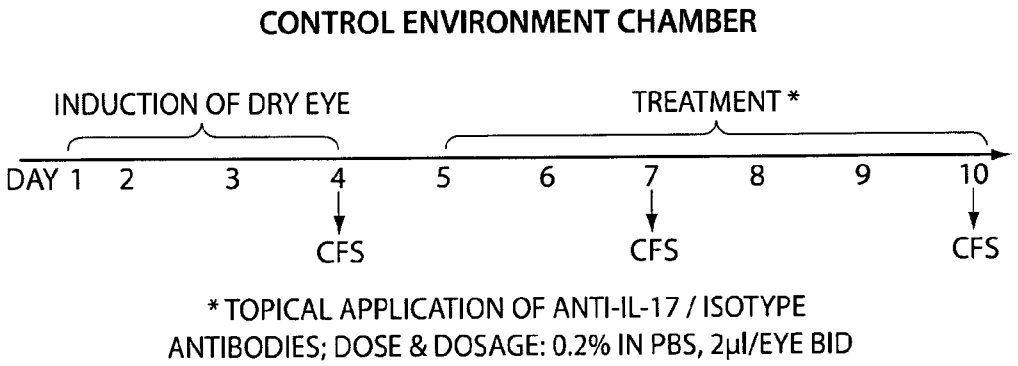

CONTROL ENVIRONMENT CHAMBER
INDUCTION OF DRY EYE
TREATMENT *
DAY 1 2 3 4 5 6 7 8 9 10
CFS
CFS
CFS
* TOPICAL APPLICATION OF ANTI-IL-17 / ISOTYPE ANTIBODIES; DOSE & DOSAGE: 0.2% IN PBS, 2µl/EYE BID

Fig. 8A

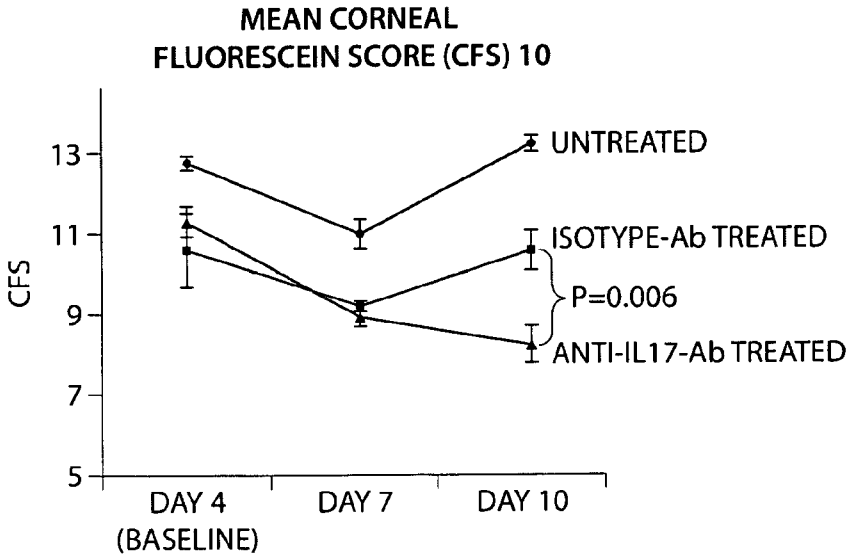

MEAN CORNEAL FLUORESCEIN SCORE (CFS) 10
CFS
13
11
9
7
5
UNTREATED
ISOTYPE-Ab TREATED
P=0.006
ANTI-IL17-Ab TREATED
DAY 4 (BASELINE)
DAY 7
DAY 10

Fig. 8B

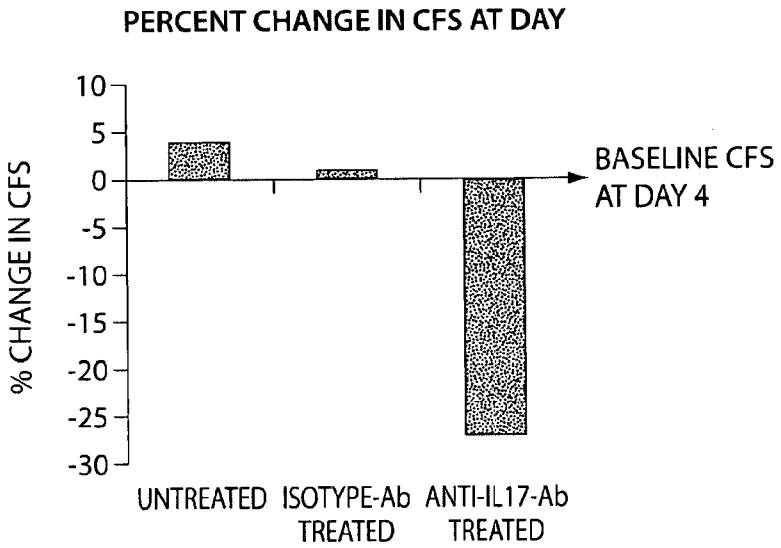

PERCENT CHANGE IN CFS AT DAY
% CHANGE IN CFS
10
5
0
-5
-10
-15
-20
-25
-30
BASELINE CFS
AT DAY 4
UNTREATED
ISOTYPE-Ab
TREATED
ANTI-IL17-Ab
TREATED

Fig. 8C

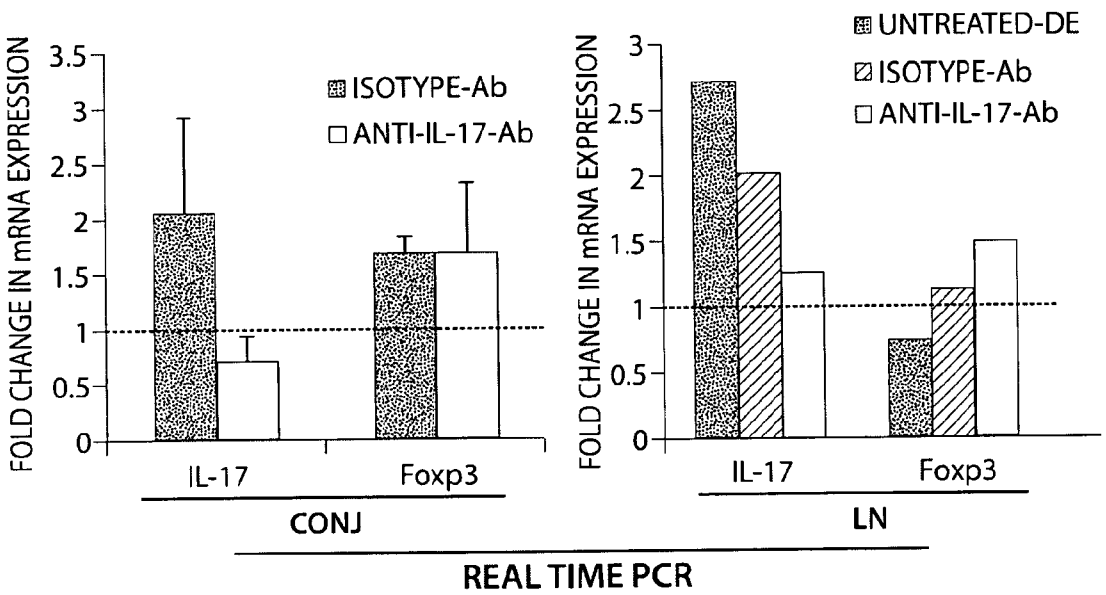

FOLD CHANGE IN mRNA EXPRESSION
3.5
3
2.5
2
1.5
1
0.5
0
ISOTYPE-Ab
ANTI-IL-17-Ab
IL-17
Foxp3
CONJ
FOLD CHANGE IN mRNA EXPRESSION
3
2.5
2
1.5
1
0.5
0
UNTREATED-DE
ISOTYPE-Ab
ANTI-IL-17-Ab
IL-17
Foxp3
LN
REAL TIME PCR

Fig. 9

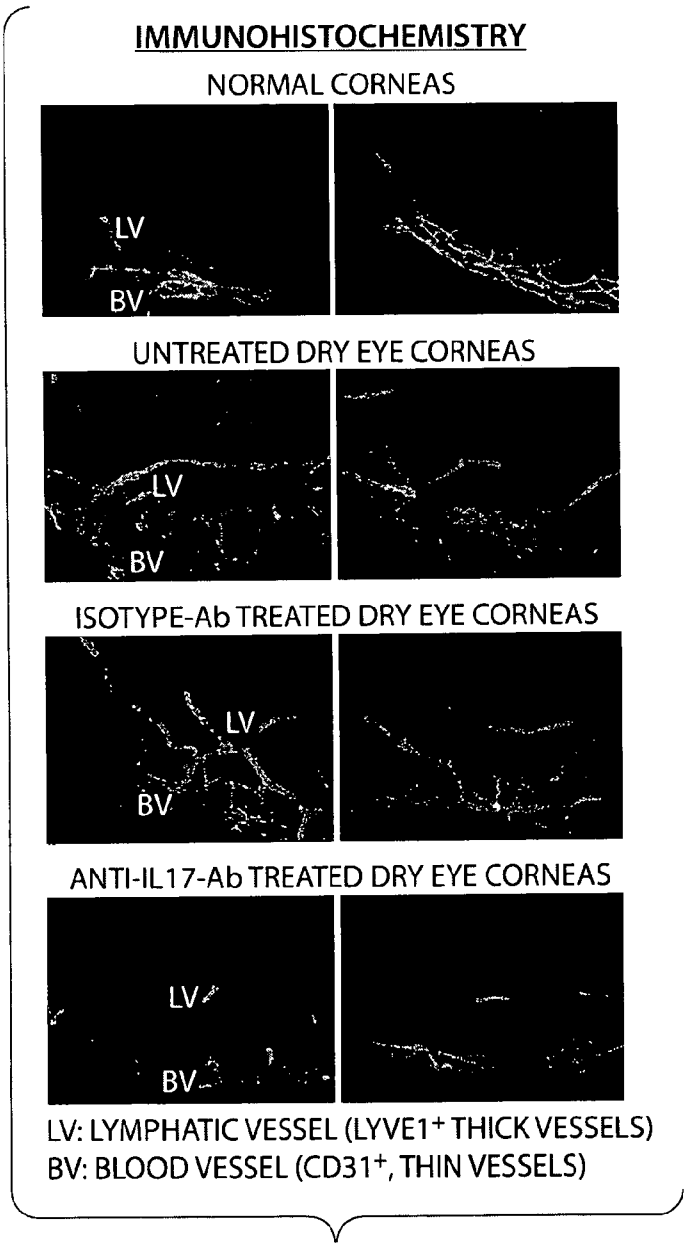

IMMUNOHISTOCHEMISTRY
NORMAL CORNEAS
LV
BV
UNTREATED DRY EYE CORNEAS
LV
BV
ISOTYPE-Ab TREATED DRY EYE CORNEAS
LV
BV
ANTI-IL17-Ab TREATED DRY EYE CORNEAS
LV
BV
LV: LYMPHATIC VESSEL (LYVE1+ THICK VESSELS)
BV: BLOOD VESSEL (CD31+, THIN VESSELS)

Fig. 10A

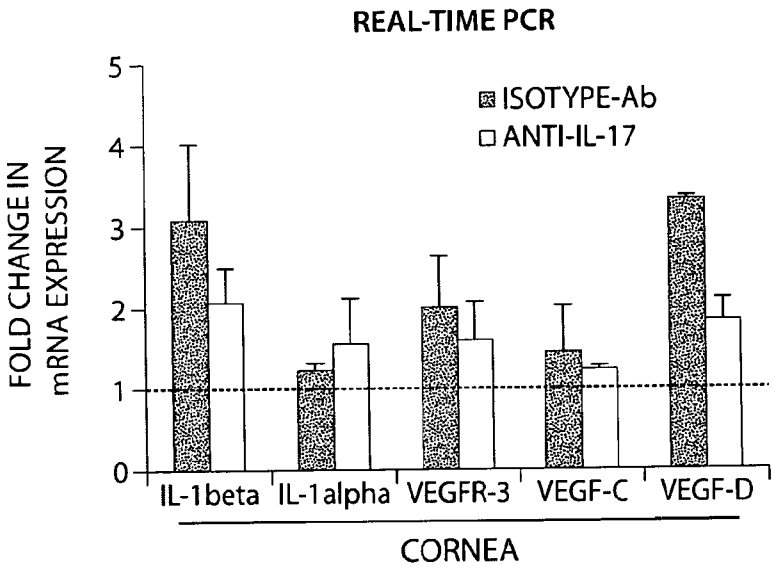

REAL-TIME PCR
ISOTYPE-Ab
ANTI-IL-17
FOLD CHANGE IN mRNA EXPRESSION
5
4
3
2
1
0
IL-1beta
IL-1alpha
VEGFR-3
VEGF-C
VEGF-D
CORNEA

Fig. 10B

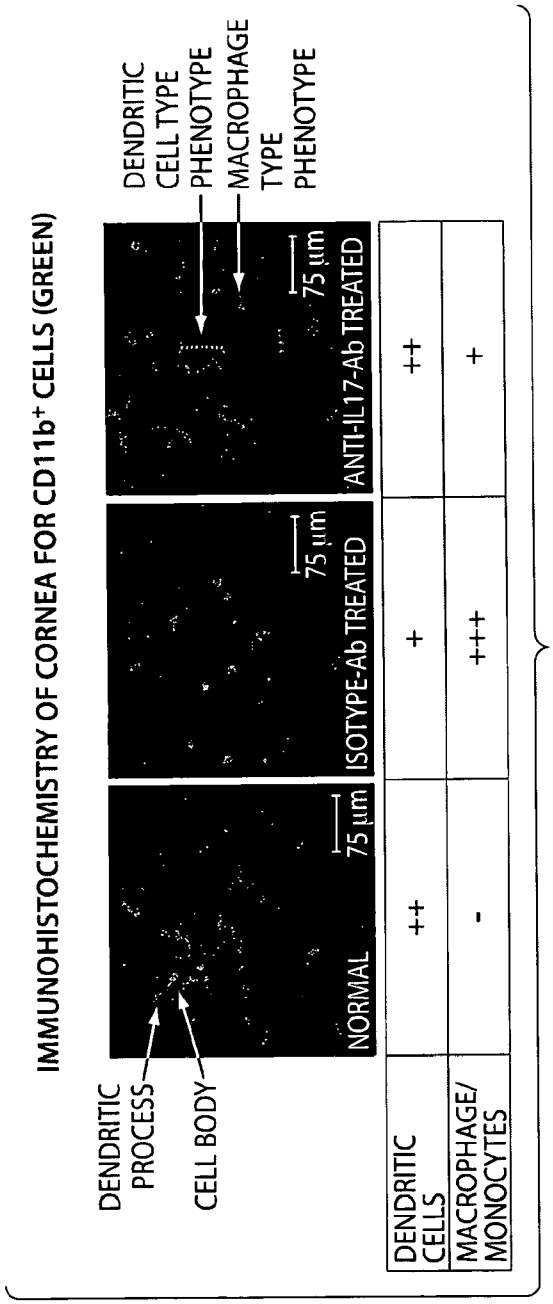

IMMUNOHISTOCHEMISTRY OF CORNEA FOR CD11b+ CELLS (GREEN)
DENDRITIC PROCESS
CELL BODY
NORMAL
ISOTYPE-Ab TREATED
ANTI-IL17-Ab TREATED
75 µm
DENDRITIC CELL TYPE PHENOTYPE
MACROPHAGE TYPE PHENOTYPE
DENDRITIC CELLS
MACROPHAGE/ MONOCYTES
++
-
+
+++
++
+

Fig. 11

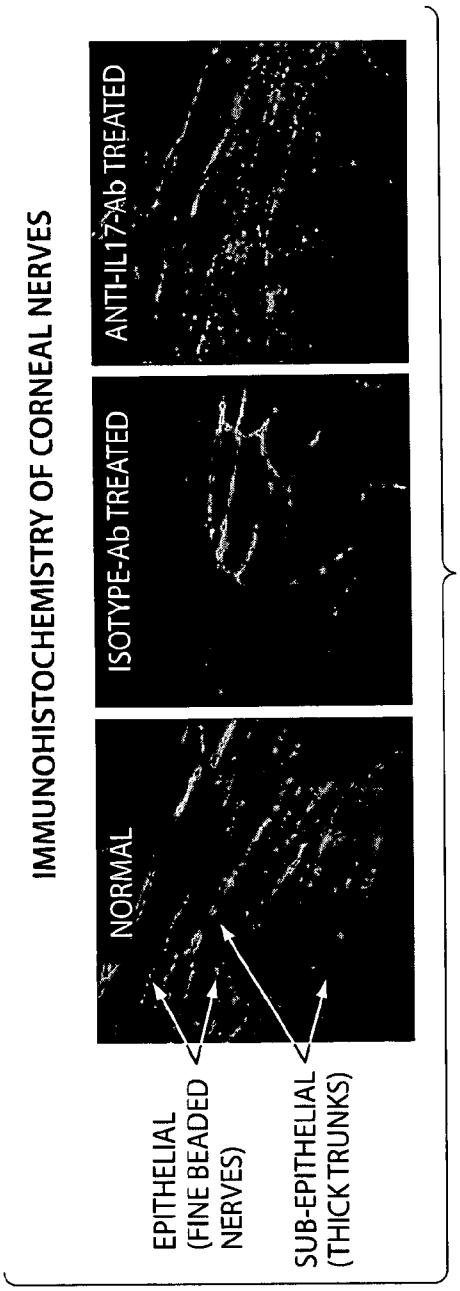

IMMUNOHISTOCHEMISTRY OF CORNEAL NERVES
NORMAL
ISOTYPE-Ab TREATED
ANTI-IL17-Ab TREATED
EPITHELIAL (FINE BEADED NERVES)
SUB-EPITHELIAL (THICK TRUNKS)

Fig. 12

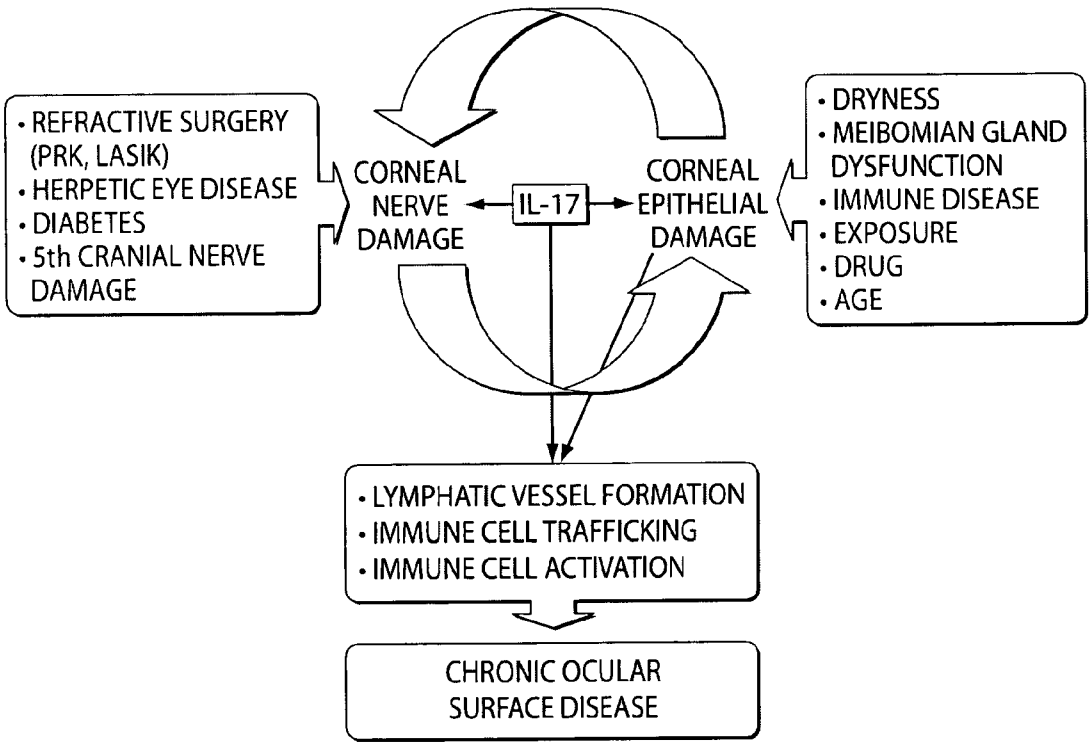

• REFRACTIVE SURGERY (PRK, LASIK)
• HERPETIC EYE DISEASE
• DIABETES
• 5th CRANIAL NERVE DAMAGE
CORNEAL NERVE DAMAGE
IL-17
CORNEAL EPITHELIAL DAMAGE
• DRYNESS
• MEIBOMIAN GLAND DYSFUNCTION
• IMMUNE DISEASE
• EXPOSURE
• DRUG
• AGE
• LYMPHATIC VESSEL FORMATION
• IMMUNE CELL TRAFFICKING
• IMMUNE CELL ACTIVATION
CHRONIC OCULAR SURFACE DISEASE

Fig. 13

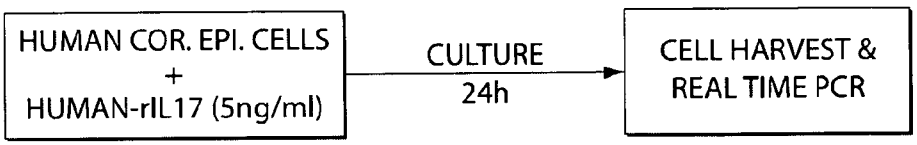


Fig. 14A

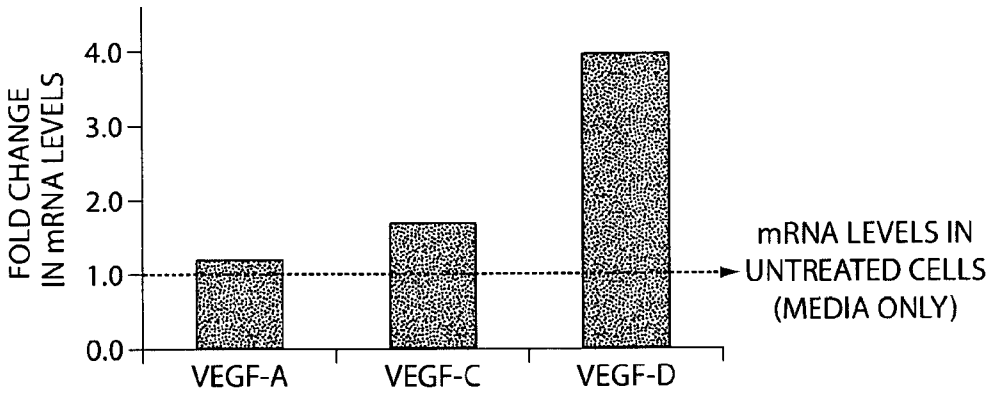
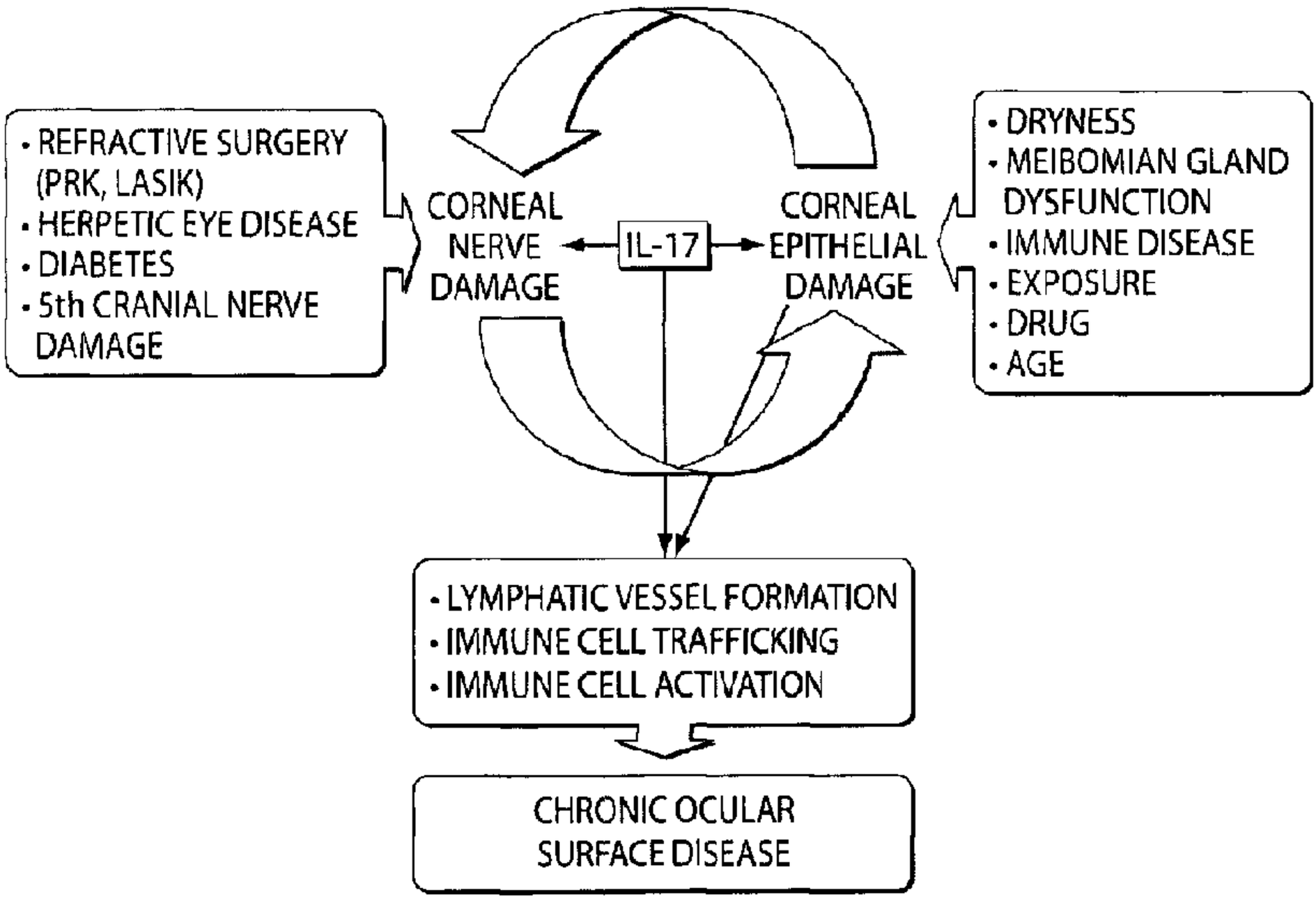


Fig. 14B


• REFRACTIVE SURGERY (PRK, LASIK)
• HERPETIC EYE DISEASE
• DIABETES
• 5th CRANIAL NERVE DAMAGE
CORNEAL NERVE DAMAGE
IL-17
CORNEAL EPITHELIAL DAMAGE
• DRYNESS
• MEIBOMIAN GLAND DYSFUNCTION
• IMMUNE DISEASE
• EXPOSURE
• DRUG
• AGE
• LYMPHATIC VESSEL FORMATION
• IMMUNE CELL TRAFFICKING
• IMMUNE CELL ACTIVATION
CHRONIC OCULAR SURFACE DISEASE