(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 273 988 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
09.09.2015 Bulletin 2015/37

(21) Application number: **09733334.8**

(22) Date of filing: **17.04.2009**

(51) Int Cl.:
A61K 31/00 *(2006.01)*

(86) International application number:
PCT/US2009/041021

(87) International publication number:
WO 2009/129497 (22.10.2009 Gazette 2009/43)

(54) **L-DOPA FOR TREATING AGE-RELATED MACULAR DEGENERATION**

L-DOPA ZUR BEHANDLUNG DER ALTERBSEDINGTEN MAKULADEGENERATION

L-DOPA POUR LE TRAITEMENT DE LA DÉGÉNÉRESCENCE MACULAIRE LIÉE A L AGE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK TR

(30) Priority: **18.04.2008 US 124624 P**

(43) Date of publication of application:
19.01.2011 Bulletin 2011/03

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Description

Background

[0001] Age-related macular degeneration ("AMD") is an aging-associated disease resulting in the loss of vision in the macula (the center of the visual field) because of damage to the retina. AMD is a prevalent disorder of the aged, with approximately 10% of patients 66 to 74 years and 30% of patients 75 to 85 years of age having some level of macular degeneration. Currently there is no effective treatment available for most patients with AMD, and no early stage intervention.

[0002] International patent application WO 03/070269 relates to 5,6-dihydroxyindole (DHI), 5,6-dihydroxyindole-2-carboxylic acid (DHICA) and/or 5-S-cysteinyldopa (CD) as medicaments, as well as their use, and the use of tyrosinase for the preparation of a medicament for prophylaxis or therapy of diseases induced by oxidative stress.

Summary of the Invention

[0003] The present invention provides an agonist of the OA1 receptor for use in treating or preventing age-related macular degeneration (AMD), wherein the agonist of the OA1 receptor is L-DOPA.

[0004] The L-DOPA may be provided as a composition comprising:

(a) an amount effective of L-DOPA for treating or limiting development of AMD; and
(b) an amount effective for treating or limiting development of AMD of a composition comprising a source of vitamin C, a source of vitamin E, a source of vitamin A, a source of zinc, and a source of copper.

Brief Description of the Figures

[0005]

Figure 1(a-c) Western blot analysis of proteins bound (B) or unbound (U) to strepavidin-conjugated beads after biotinylation of RPE *in situ*, cultured RPE (b), or COS cells transfected to express OA1-GFP (c). Blots were probed to visualize OA1 and actin after cell surface biotinylation and fractionation using streptavidin-conjugated beads. For cultured cells (b, c) cells were either maintained in 500 μM (normal DMEM) or 1 μM tyrosine for 3 days prior to analysis.
Figure 1(d) Quantification of western blot analysis by densitometry. OA1 densitometry is shown as the % of the control for paired cell cultures, transfected then split into 2 equal groups, one of which was the control, maintained in normal DMEM (control). The other group was maintained in 1 μM tyrosine DMEM (LT) until harvest. Paired t-test analysis was used to test whether the difference was significant, and * denotes $p<0.001$. Actin, analyzed the same way showed no differences, and $p=0.724$.
Figure 1(e-f) Composite confocal microscopy of pigmenting RPE cells maintained in normal DMEM (e) or 1 μM tyrosine (f) then stained with anti-OA1 antibodies and imaged at 20x. Bar = 25 μm.
Figure 2(a) Representative traces of $[Ca^{2+}]i$ during the time course of the standard experimental protocol in transfected and untransfected CHO cells. After establishment of a stable baseline for 3 minutes, the test agent was added at 1 μM. At 5 minutes, KCl was added to serve as a control that the cells were Fura-2 loaded and patent. Identical protocols were performed for both transfected cells and paired untransfected cells.
Figure 2(b) Summary data for $[Ca^{2+}]i$ in response to tyrosine, dopamine, and L-DOPA in transfected and untransfected CHO cells. Untransfected cells are shown with L-DOPA treatment. The experimental control of membrane depolarization with KCl is also shown.
Each bar represents data collected from at least 10 experiments and is presented as the mean change from baseline $[Ca^{2+}]i$ after test agent addition. Error bars represent S.D., and t-test analyses were used to test for significant differences, * denotes $p<0.01$.
Analysis of pertussis toxin sensitivity of $[Ca^{2+}]i$ increase in cells transfected to express OA1 or RPE that express the natural protein. Data represent mean of at least 6 experiments.
Figure 2(c) Analysis of pertussis toxin sensitivity of $[Ca^{2+}]i$ increase in cells transfected to express OA1 or RPE that express the natural protein. Data represent mean of at least 6 experiments for each group of transfected cells and 20 individual experiments for each the treated and untreated RPE with endogenous OA1 expression. T-tests analyses were used to test for significant differences, and * denotes $p<0.01$.
Figure 2 (d) cAMP was measured in CHO transfected to express OA1. The control group represents transfected but untreated CHO cells and the basal level of cAMP in those cells. Cells were treated with 1.0 μM L-DOPA; 0.1 μM forskolin, L-DOPA + 0.1 μM forskolin, and as a positive control 1 μM forskolin. Results represent the mean cAMP levels observed in at least 6 experiments in which all experimental groups were analyzed in a paired fashion

using replicate monolayers in the same culture plate. Error bars represent the S.D. of each group, and the only significant difference observed was the increase in cAMP levels after forskolin treatment.

Figure 3(a) Binding kinetics between OA1 and L-DOPA were determined using radiolabeled ligand binding assays. Results represent data collected from 5 such experiments and are presented as mean specific binding +/- SEM. The hyperbolic curve fit exhibited an R^2 value of 0.994, Kd was determined to be $9.34x10^{-6}$M +/ $1.14x10^{-6}$M.

Figure 3(b) Comparative binding of 5μM [H^3] L-DOPA to OA1 transfected CHO cells was compared in the presence of 1.0 mM dopamine, tyrosine, or L-DOPA. The data represent mean total binding +/- S.D. for each group. * denotes $p<0.05$ when comparing the results between the control group to the binding in the presence of the potential competitive ligands.

Figure 3(c) Competitive interaction between 5μM [H^3] L-DOPA and dopamine were assessed to determine whether dopamine functions as an antagonist of OA1 activity. Results indicate that dopamine and L-DOPA compete for the same OA1 binding site, and the data fits the binding model with an r^2 value of 0.95. The Ki for dopamine was 2.388 +/- 0.266 μM (mean +/- SEM), similar to the Kd for L-DOPA.

Figure 3(d) Dose-dependent OA1 signaling through OA1. Data represent mean increase in $[Ca^{2+}]_i$ elicited by L-DOPA treatment of the cells at the concentrations given (n=6 for each dose). T-test analyzes were used to compare between the responses achieved at each dose, and * denotes $p<0.01$ for the comparison at 1 and 10 μM.

Figure 3(e) Scatchard plot illustrating the kinetics of a single site binding relationship based on Figure 3(a).

Figure 4(a-h) All images represent 2 μm thick confocal sections of CHO cells transfected to express OA1-GFP. β-arrestin was visualized using immuno fluorescence methods.

Prior to addition of L-DOPA (a-c) and after treatment with 1 μM L-DOPA (d-f), and the merged images (c, f) illustrate regions where the two proteins co-localize, at the resolution of white light imaging. (g,h) are low magnification of field of transfected CHO cells, with two transfected cells visible (arrows) (g). The remainder of the cell population is visualized using antibodies to β-arrestin (h) to illustrate that β-arrestin recruitment to the membrane only occurred in the OA1 expressing cells (arrows).

Figure 5 (a) PEDF concentrations were determined by ELISA of cell conditioned medium. RPE cells were control cells, without L-DOPA treatment, or OA1 stimulated cells that were treated with 1 μM L-DOPA prior to being maintained for 3 days in normal DMEM. Data are presented as the mean of 3 experiments conducted in triplicate, error bars represent S.D, and * denotes $P<0.01$ using a paired t-test.

Figure 5(b) PEDF concentrations in conditioned medium from pigmenting RPE determined by ELISA. Cells were either control pigmenting RPE cultures or paired cultures treated with phenylthiourea (PTU) at 200 μM. Data are presented as the mean of 3 experiments conducted in triplicate, error bars represent S.D, and * denotes $P<0.01$ using a paired t-test.

Figure 5(c) PEDF concentrations in conditioned medium of pigmented RPE cells treated with PTU then treated with L-DOPA to stimulate OA1 signaling. ELISA assays were conducted prior to PTU treatment, then after PTU treatment, and then from the same cultures after L-DOPA stimulation. Results are presented as mean +/- S.D. of the value achieved related to that culture of cells. * denotes $p<0.01$ when comparing PTU to the control (same culture tested prior to PTU), and L-DOPA/PTU compared to the PTU sample from that same culture.

Figure 6(a) Data represents mean +/- SEM bound [3H]-L-DOPA in all fractions, total, specific and non-specific. Non-specific binding was determined by measuring radiolabeled-L-DOPA bound in the presence of excess unlabeled L-DOPA (1 mM). Specific binding at each given concentration is determined by subtracting the measured non-specific binding from the measured total binding.

Figure 6(b) The figure illustrates competitive interaction between tyrosine and L-DOPA, measured using increasing concentrations of tyrosine and 5μM [H^3] L-DOPA. Each data point represents the mean data from 5 replicate wells, and the error bars are S.D. Data illustrate that tyrosine competes for binding with L-DOPA, but with a low affinity. The results suggest tyrosine has a Ki of 52.9 μM, and fits the single site binding model with an r^2 value of 0.85. Saturation could not be achieved because of the limited solubility of tyrosine.

Figure 7 Western blot and graphical representation of PEDF secretion in wild-type vs OA deficient mice.

Figure 8(a) is a graphical representation of data demonstrating that L-DOPA supplementation increases retinal ganglion cell numbers compared to what is expected in a normal wild-type mouse.

Figure 8(b) is a graphical representation of data demonstrating that L-DOPA supplementation increases photoreceptor numbers compared to what is expected in a normal wild-type mouse.

Figure 8(c) is a Western blot showing PEDF detection in 2 wild-type and 2 OA1 -/y mice.

Detailed Description of the Invention

[0006] Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: Molecular Cloning: A Laboratory Manual (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), Gene Expression Technology (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic

Press, San Diego, CA), "Guide to Protein Purification" in Methods in Enzymology (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); PCR Protocols: A Guide to Methods and Applications (Innis, et al. 1990. Academic Press, San Diego, CA), Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed. (R.I. Freshney. 1987. Liss, Inc. New York, NY), Gene Transfer and Expression Protocols, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

[0007] As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise.

[0008] The present invention provides an agonist of the OA1 receptor for use in treating or preventing age-related macular degeneration (AMD), wherein the agonist of the OA1 receptor is L-DOPA.

[0009] The human *Oa1* gene, is found on the X chromosome, and has been shown to encode a 404 amino acid protein OA1 (**SEQ ID NO:2**), likely to be a G-protein coupled receptor (GPCR) [12,13] based upon sequence analysis [14]. As disclosed in detail herein, the inventors have identified the OA1 signaling pathway as a critical determinant of neurosensory retina survival, such that stimulation of this pathway will provide treatment for AMD as well as a means to limit AMD development for those at potential risk. While not being bound by any mechanism, the inventors believe that OA1 and tyrosinase participate in an autocrine loop through L-DOPA that regulates the secretion of at least one potent neurotrophic factor, PEDF. Thus administration of L-DOPA can be used to stimulate OA1 activity and thus upregulate PEDF expression, making it a valuable therapeutic to treat and limit development of AMD.

[0010] The subject preferably is a human.

[0011] As used herein for all aspects and embodiments of the invention, "AMD" means an aging-associated disease resulting in the loss of vision in the macula (the center of the visual field) because of damage to the retina know as Age-related Macular Degeneration. As used herein, AMD encompasses both wet and dry AMD, described in more detail below.

[0012] AMD begins with characteristic drusen (yellow deposits) in the macula between the retinal pigment epithelium and the underlying choroid. Most people with these early changes (referred to as age-related maculopathy) have good vision. People with drusen can go on to develop advanced AMD. The risk is considerably higher when the drusen are large and numerous and associated with disturbance in the pigmented cell layer under the macula.

[0013] Subjects with age-related maculopathy may progress to either of the two main forms of advanced AMD, each of which can be treated or be limited in its development using the methods of the invention. 'Wet" AMD causes vision loss due to abnormal blood vessel growth in the choriocapillaries, through Bruch's membrane, ultimately leading to blood and protein leakage below the macula. Bleeding, leaking, and scarring from these blood vessels eventually causes irreversible damage to the photoreceptors and rapid vision loss if left untreated. "Dry" AMD occurs when light-sensitive cells in the macula slowly break down, gradually causing vision loss in the affected eye. Blurring in AMD is probably due to the accumulation of drusen under the retinal pigment epithelium (RPE) which alters to focal properties of the photoreceptors by moving them out of the plane of focus.

[0014] Dry AMD may occur in one or both eyes, and can advance from age-related maculopathy into intermediate or advanced stages of dry AMD.

[0015] Intermediate Dry AMD: Either many medium-sized drusen or one or more large drusen. Some people see a blurred spot in the center of their vision. More light may be needed for reading and other tasks.

[0016] Advanced Dry AMD: In addition to drusen, a breakdown of light-sensitive cells and supporting tissue in the central retinal area. This breakdown can cause a blurred spot in the center of vision. Over time, the blurred spot may get bigger and darker, taking more of the central vision; may have difficulty reading or recognizing faces until they are very close to you.

[0017] AMD symptoms include, but are not limited to blurred/reduced central vision, central scotomas (shadows or missing areas of vision), trouble discerning one dark color from another dark color and/or one light color from another light color; slow recovery of visual function after exposure to bright light, a loss in contrast sensitivity, so that contours, shadows and color vision are less vivid, retinal pigment epithelial (RPE) disturbance (including pigment clumping and/or dropout), RPE detachment, geographic atrophy, subretinal neovascularization, and disciform scar, and distorted vision (metamorphopsia), such that a grid of straight lines appears wavy and parts of the grid may appear blank Symptoms of dry AMD and wet AMD are generally similar early during disease-progression, and thus it may not be possible to determine which early-stage patients will develop dry vs. wet forms of AMD. Dry AMD develops as 'geographic atrophy', and early AMD become 'wet' AMD when new blood vessels sprout.

[0018] As used herein, "treat" or "treating" AMD means accomplishing one or more of the following: (a) reducing the severity of AMD; (b) limiting or preventing development of one or more symptoms characteristic of AMD, as described above; (c) inhibiting worsening of one or more symptoms characteristic of AMD, as described above; (d) limiting or preventing recurrence of AMD in patients that have previously had the disorder(s); and (e) limiting or preventing recurrence of one or more symptoms in patients that were previously symptomatic for AMD. Such treating includes treating of wet AMD and dry AMD.

[0019] As used herein, the term "limiting development of" AMD means to prevent or to minimize development of AMD in individuals at risk of developing AMD, as well as limiting progression of age-related maculopathy to AMD (wet or dry),

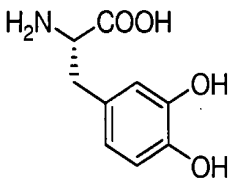
or intermediate dry AMD to advanced dry or 'wet' AMD. In one preferred embodiment, the treatment comprises treating a subject with drusen accumulation (ie: age-related maculopathy), to limit development of AMD. In another preferred embodiment, the treatment comprises treating a subject with an amount effective of the OA1 agonist L-DOPA to decrease the rate of lines of loss of vision relative to a non-treated AMD subject, or subject at risk of AMD. In another preferred embodiment, the treatment comprises treating a subject with wet AMD, or at risk of developing wet AMD, an amount effective of the OA1 agonist L-DOPA to decrease the rate and number of new blood vessel formation. As discussed in more detail below, OA1 stimulation causes the RPE to increase PEDF secretion, and PEDF is a potent anti-angiogenic factor. Thus, OA1 stimulation strategies may stop new blood vessel development in 'wet' AMD, in addition to its effects on retinal development discussed herein.

[0020] In another preferred embodiment, the treatment comprises treating a subject that has blurred or reduced central vision with an amount of the OA1 agonist L-DOPA effective to increase the lines of visual acuity in one or both eyes. In this embodiment, the lines of visual acuity are as measured by the standard Snellen test, where the increase or decrease in 'lines' of visual acuity are based on which smallest 'line' on a Snellen chart a patient can read clearly.

[0021] "Subjects at risk of developing AMD" means anyone with any risk factor for development of AMD, including but not limited to being over 50 years old (in various preferred embodiments, over 60 years old, over 65 years old, over 70 years old, or over 75 years-old), presence of drusen deposits, Caucasian race, having a blood relative that has or had AMD, a mutation in the complement factor H gene (CFH) of (Tyr402His), Arg80Gly variant of the complement protein C3 gene, hypertension, high cholesterol levels, obesity, smoking, a high fat intake, and mutations in the fibulin 5 gene. Thus, in a preferred embodiment, the subject to be treated has one or more of these risk factors, particularly in treatments for limiting development of AMD.

[0022] The phrase "therapeutically effective amount," as used herein, refers to an amount that is sufficient or effective to limit development of or treat (prevent the progression of or reverse) AMD. The appropriate dosage range depends on the choice of the compound, the route of administration, the nature of the formulation, the nature of the subject's condition, and the judgment of the attending practitioner. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art.

[0023] L-DOPA is [2-amino-3-(3,4-dihydroxyphenyl)propanoic acid] known for use in treating Parkinson's, and has the following structure.



[0024] L-DOPA is commercially available and methods for its synthesis are known to those of skill in the art.

[0025] While not being bound by a specific mechanism of action, the inventor believes that L-DOPA binding to OA1 involves two sites of binding, one involving one or both hydroxyl groups, and one involving the carboxylic acid group.

[0026] In one embodiment of the invention, the treatment or prevention may comprise administering a further therapeutic compound to the subject, including but not limited to an L-amino acid decarboxylase inhibitor, such as carbidopa or benserazide. Such L-amino acid decarboxylase inhibitors can be used, for example, to increase plasma half-life of L-DOPA and reduce conversion of L-DOPA to dopamine peripherally, which reduces side effects of L-DOPA treatment. In another embodiment, the treatment or prevention may further comprise administering one or more other compounds useful for treating or limiting development of AMD, including but not limited to anti-angiogenic therapeutics, such as anti-vascular endothelial growth factor (VEGF) agents, including but not limited to VEGF antibodies (or fragments thereof) such as ranibizumab or bevacizumab, or VEGF aptamers, such as pegaptanib. In another embodiment, the L-DOPA may be present in a more complex mixture, such as in a nutritional supplement containing L-DOPA.

[0027] In a preferred embodiment, the L-DOPA may be used in the form of a dietary supplement. Such a supplement may combine any one or more further components that might be beneficial in treating or limiting development of AMD. In one preferred embodiment, L-DOPA is combined with a combination of vitamin C source, vitamin E source, Vitamin A source, zinc source, and a copper source, disclosed in US Patent No. 6,660,297 as useful in treating AMD. Any suitable amount of each of these additional components can be used in combination with L-DOPA in carrying out the treatment or prevention described in relation to the invention. In a further preferred embodiment, this combination may further comprise lutein and/or zeaxanthin in an amount suitable to provide further protective retinal effects, preferably between 1 mg and 100 mg; between 1 mg and 50 mg, between 2 mg and 25 mg, or between 2 mg and 10 mg per day. In a further preferred embodiment of any of the above preferred embodiments, this combination may further comprise docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA) in an amount suitable to provide further protective retinal effects,

preferably between 250 mg and 1000 mg; between 300 mg and 750 mg, between 350 mg and 750 mg, or between 350 mg and 650 mg per day. The use of such compositions for treating AMD patients is discussed, for example, at web site www.areds2.org/ and links therein.

[0028] Ascorbic acid is the preferred source of vitamin C, although other sources such as for example sodium ascorbate could alternatively be used.

[0029] Dl-alpha tocopheryl acetate is the preferred source of vitamin E, although other sources of vitamin E, such as for example trimethyl tocopheryl acetate and/or vitamin E succinate, may be used in the alternative.

[0030] Beta-carotene is preferred in the subject composition due to its ready commercial availability although alternative carotenoid proforms of vitamin A could likewise be used.

[0031] Zinc is preferred in the form of zinc oxide in subject tablets due to the fact zinc oxide provides the most concentrated form for elemental zinc and is well tolerated in the digestive system. However, other forms of zinc such as for example zinc gluconate may alternatively be used or be used in combination with zinc oxide in the subject composition.

[0032] Copper in the form of cupric oxide is preferred in the subject tablets to help prevent zinc induced copper deficiency anemia, although other forms of copper such as for example copper gluconate may alternatively be used or used in combination with cupric oxide in the subject composition.

[0033] In a preferred embodiment, the amounts of each of these other components (on a per day basis) is as follows:

between 450 mg and 600 mg vitamin C (approximately 7-10 times the recommended daily allowance (RDA))
between 400 IU and 540 IU vitamin E (approximately 13-18 times the RDA);
between 17.2 mg and 28 mg beta carotene (approximately 6-10 times the RDA of vitamin A; beta carotene is a prodrug of vitamin A);
between 68 mg and 100 mg zinc (approximately 4-7 times the RDA for zinc); and
between 1.6 mg and 2.4 mg copper.

[0034] In a further preferred embodiment, the amounts of each of these other components (on a per day basis) is as follows:

500 mg Vitamin C;
400 IU Vitamin E;
0 mg or 15 mg beta carotene;
25 mg or 80 mg zinc oxide; and
2 mg cupric oxide.

[0035] In a further preferred embodiment, that may be combined with any other embodiments herein, other ingredients believed to be of benefit in maintaining eye health may likewise be combined with L-DOPA, including but not limited to lutein and/or zeaxanthin in an amount suitable to provide further protective retinal effects, preferably between 1 mg and 100 mg; between 1 mg and 50 mg, between 2 mg and 25 mg, or between 2 mg and 10 mg per day; and/or docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA) in an amount suitable to provide further protective retinal effects, preferably between 250 mg and 1000 mg; between 300 mg and 750 mg, between 350 mg and 750 mg, or between 350 mg and 650 mg per day. Further examples of additional compounds that may optionally be used include but are not limited to alpha-lipoic acid and, phenolic compounds such as for example but not limited to oligomeric proanthocyanidins, anthocyanosides and combinations thereof.

[0036] L-DOPA can be administered individually or in combination, usually in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art. L-DOPA can be administered as the sole active pharmaceutical agent, or it can be used in combination with one or more other compounds useful for carrying out the treatment or prevention described in relation to the invention, including but not limited to anti-angiogenic therapeutics such as VEG-F, and L-amino acid decarboxylase inhibitors, such as carbidopa and benserazide. When administered as a combination, combination can be formulated as separate compositions that are given at the same time or different times, or can be given as a single composition.

[0037] The L-DOPA may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.,* solutions, suspensions, or emulsions). The L-DOPA may be applied in a variety of solutions and may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

[0038] The L-DOPA may be administered by any suitable route, including but not limited to oral, topical (including but not limited to eye drops and ophthalmic ointments), parenteral, intranasal, pulmonary, or rectal in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound

of the invention and a pharmaceutically acceptable carrier. L-DOPA may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing L-DOPA may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0039] Eye drops can be prepared using any technique in the art, including but not limited to using a tonicity agent such as sodium chloride or concentrated glycerin, a buffer such as sodium phosphate or sodium acetate, a surfactant such as polyoxyethylene sorbitan monooleate, polyoxyl 40 stearate or polyoxyethylene hydrogenated castor oil, a stabilizer such as sodium citrate or sodium edetate, a preservative such as benzalkonium chloride or paraben as needed. The pH of the eye drops is preferably in the range of from 4 to 8. Ophthalmic ointments can be prepared with a generally used base such as white soft paraffin or liquid paraffin.

[0040] L-DOPA intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide palatable preparations. Tablets contain the L-DOPA in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

[0041] Formulations for oral use may also be presented as hard gelatin capsules wherein the L-DOPA is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0042] Aqueous suspensions contain the L-DOPA in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0043] Oily suspensions may be formulated by suspending the L-DOPA in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0044] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0045] Pharmaceutical compositions for use in the treatment or prevention described in relation to the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0046] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium

chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0047] Specific methods for intranasal administration of L-DOPA are known in the art; see, for example, Kao et al., Pharmaceutical Research 17(8):978-984 (2000).

[0048] The dosage range depends on the choice of the compound, the route of administration, the nature of the formulation, the nature of the subject's condition, and the judgment of the attending practitioner. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art. In certain embodiments, L-DOPA can be administered at dosages of between 10 mg/day and 1500 mg/day; in various preferred embodiments administration can be between 20 mg and 1200 mg/day, 50 mg and 1000 mg/day, 100 mg and 500 mg/day, and 200 mg and 400 mg/day.

[0049] Pharmaceutical compositions containing the compounds described herein are administered to an individual in need thereof. In a preferred embodiment, the subject is a mammal; in a more preferred embodiment, the subject is a human. In therapeutic applications, compositions are administered in an amount sufficient to carry out the treatment or prevention described in relation to the invention. Amounts effective for these uses depend on factors including, but not limited to, the nature of the compound (specific activity, etc.), the route of administration, the stage and severity of the disorder, the weight and general state of health of the subject, and the judgment of the prescribing physician. The active compound is effective over a wide dosage range. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the above relevant circumstances. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way.

[0050] The L-DOPA for use in the present invention may be provided as a composition comprising:

(a) an amount effective of L-DOPA for treating or limiting development of AMD; and
(b) an amount effective for treating or limiting development of AMD of a composition comprising a source of vitamin C, a source of vitamin E, a source of vitamin A, a source of zinc, and a source of copper.

[0051] The amount of L-DOPA in the compositions is suitable to provide for administration at dosages of between 10 mg/day and 1500 mg/day; in various preferred embodiments administration can be between 20 mg and 1200 mg/day, 50 mg and 1000 mg/day, 100 mg and 500 mg/day, and 200 mg and 400 mg/day.

[0052] Ascorbic acid is the preferred source of vitamin C in the subject tablets, although other sources such as for example sodium ascorbate could alternatively be used. Dl-alpha tocopheryl acetate is the preferred source of vitamin E in the subject tablets although other sources of vitamin E, such as for example trimethyl tocopheryl acetate and/or vitamin E succinate, may be used in the alternative. Beta-carotene is preferred in the subject composition due to its ready commercial availability although alternative carotenoid proforms of vitamin A could likewise be used. Zinc is preferred in the form of zinc oxide in subject tablets due to the fact zinc oxide provides the most concentrated form for elemental zinc and is well tolerated in the digestive system. However, other forms of zinc such as for example zinc gluconate may alternatively be used or be used in combination with zinc oxide in the subject composition. Copper in the form of cupric oxide is preferred in the subject tablets to help prevent zinc induced copper deficiency anemia, although other forms of copper such as for example copper gluconate may alternatively be used or used in combination with cupric oxide in the subject composition.

[0053] In one preferred embodiment, composition "b" provides a formulation suitable to permit ingestion of the following amounts of each component:

Ascorbic acid: at least 450 mg;
dl-alpha tocopheryl acetate: 400 IU;
beta carotene: 17.2 mg;
zinc oxide: 68 mg; and
cupric oxide: 1.6 mg.

[0054] In one preferred embodiment, composition "b" provides a formulation suitable to permit ingestion of the following amounts of each component:

500 mg Vitamin C;
400 IU Vitamin E;
0 mg or 15 mg beta carotene;
25 mg or 80 mg zinc oxide; and
2 mg cupric oxide.

[0055] The preferred daily dosage of the subject composition as specified above may be administered in the form of 1, 2, 3, 4, or more dosage forms according to any suitable route of administration as disclosed above. In preferred embodiments, the dosage form is an oral or topical dosage form, according to any embodiment of such dosage forms described herein. In another preferred embodiment the daily dosage of the subject composition is provided in the form of one dosage form taken twice daily, for a total of two dosage forms a day, or in the form of two dosage forms taken twice daily, for a total of four dosage forms a day. Compared to taking the total daily dose once a day, twice daily dosing of half the total daily dose in one or more dosage forms per dose provides improved absorption and better maintenance of blood levels of the essential ingredients. Accordingly, if two dosage forms of the preferred formulation of the subject composition are to be ingested each day, each dosage form is formulated to preferably provide not less than approximately 225 mg ascorbic acid, approximately 200 IU dl-alpha tocopheryl acetate, approximately 8.6 mg beta-carotene, approximately 34 mg zinc oxide and approximately 0.8 mg cupric oxide upon oral administration. If four tablets of the preferred formulation of the subject composition are to be ingested each day, each tablet is formulated to preferably provide not less than approximately 112.5 mg ascorbic acid, approximately 100 IU dl-alpha tocopheryl acetate, approximately 4.3 mg beta-carotene, approximately 17 mg zinc oxide, approximately 0.4 mg cupric oxide, and between 5 mg and 750 mg of L-DOPA.

[0056] In another preferred embodiment, the compositions comprise

(a) between 5 mg and 1500 mg L-DOPA;
(b) between 450 mg and 600 mg vitamin C (approximately 7-10 times the recommended daily allowance (RDA))
(c) between 400 IU and 540 IU vitamin E (approximately 13-18 times the RDA);
(d) between 17.2 mg and 28 mg beta carotene (approximately 6-10 times the RDA of vitamin A; beta carotene is a prodrug of vitamin A);
(e) between 68 mg and 100 mg of zinc (approximately 4-7 times the RDA for zinc); and
(f) at least 1.6 mg of copper.

[0057] In various preferred embodiments, the composition may comprise between 10 mg and 1200 mg; between 25 mg and 1000 mg; between 50 mg and 500 mg, or between 100 mg and 400 mg L-DOPA.

[0058] In a further preferred embodiment, that may be combined with any other embodiments herein, other ingredients believed to be of benefit in maintaining eye health may likewise be combined with L-DOPA, including but not limited to lutein and/or zeaxanthin in an amount suitable to provide further protective retinal effects, preferably between 1 mg and 100 mg; between 1 mg and 50 mg, between 2 mg and 25 mg, or between 2 mg and 10 mg per day; and/or docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA) in an amount suitable to provide further protective retinal effects, preferably between 250 mg and 1000 mg; between 300 mg and 750 mg, between 350 mg and 750 mg, or between 350 mg and 650 mg per day. The amounts necessary in any particular dosage form to provide the recited amounts can be determined by one of skill in the art based on the teachings herein and the number of dosage forms to be administered per day.

[0059] As described above, human OA1 (**SEQ ID NO:1-2** NP 000264.1) is a G-protein coupled receptor and the inventors have herein identified L-DOPA as an OA1 ligand. As disclosed in more detail below, the inventor has discovered the existence of an autocrine loop between OA1 and tyrosinase linked through L-DOPA, and this loop includes the secretion of at least one very potent retinal neurotrophic factor (PEDF) as well as an increase in intracellular calcium concentration. OA1 is a selective L-DOPA receptor whose downstream effects govern spatial patterning of the developing retina. Thus, test compounds that selectively up-regulate PEDF expression and/or intracellular calcium concentration via stimulation of the OA1 pathway are candidate compounds for treating and/or limiting development of AMD. OA1 homologues include, but are not limited to:

Mouse: SEQ ID NO:3-4 (NM_010951);
Xenopus tropicalis: SEQ ID NOS:5-6 (NM_001011018);
Cow: SEQ ID NOS:7-8 (XM_001506318);
Rat: SEQ ID NOS: 9-10 (NM_001106958);
Platypus: SEQ ID NOS: 11-12 (XM_001506318);
Xenopus laevis: SEQ ID NOS: 13-14 (NM_001096842)
Chicken: SEQ ID NOS:15-16 (XM_416848);
Zebrafish: SEQ ID NOS: 17-18 (NM_200822);
Chimpanzee: SEQ ID NO: 19 (XR_025625);
Rhesus monkey: SEQ ID NOS:21-22 (XM_001090139; and
Macaque: SEQ ID NO: 23 (BV209253).

[0060] PEDF is pigment epithelium-derived factor (Exp Eye Res 53: 411-414), and is a known neurotrophic factor with

the potential to alter neurosensory retina development, and to inhibit blood vessel growth. PEDF homologues include, but are not limited to:

Human:	SEQ ID NOS:25-26 (NM_002615);
Rat:	SEQ ID NOS:27-28 (NM_031356);
Zebra finch:	SEQ ID NOS: 29-30 (XM_002197419);
Horse:	SEQ ID NOS:31-32 (NM_001143954);
Xenpous tropicalis:	SEQ ID NOS:33-34 (NM_203755);
Mouse:	SEQ ID NOS:35-36 (NM_011340);
Atlantic salmon:	SEQ ID NOS:37-38 (NM_001140334);
Sheep:	SEQ ID NOS:39-40 (NM_001139447);
Guinea pig:	SEQ ID NOS:41-42 (EF679792);
Cow:	SEQ ID NOS:43-44 (NM_174140);
Wild boar:	SEQ ID NOS:45-46 (NM_001078662);
Platypus:	SEQ ID NOS:47-48 (XM_001507128);
Wolf:	SEQ ID NOS: 49-50 (NM_001077588);
Macaque:	SEQ ID NOS: 51-52 (AB174277);
Chimpanzee:	SEQ ID NOS: 53-54 (XM_001154665);
Rhesus monkey:	SEQ ID NOS: 55-56 (XM_001117361); and
Flounder:	SEQ ID NOS: 57-58 (DQ115406).

[0061] The inventor has determined that OA1 signaling can be used to rescue photoreceptor and ganglion cell development in tyrosinase-deficient animals, and in the process establish the neurotrophic effect of OA1 signaling. Thus, compounds that rescue neurosensory retinal development through OA1 signaling are good candidates for AMD treatment. Described herein is the first establishment of such an animal model for AMD drug screening.

Examples: L-DOPA is an Endogenous Ligand for OA1

[0062] **Background:** Albinism is a genetic defect characterized by a loss of pigmentation. The neurosensory retina, which is not pigmented, exhibits pathologic changes secondary to the loss of pigmentation in the retina pigment epithelium (RPE). How the loss of pigmentation in the RPE causes developmental defects in the adjacent neurosensory retina has not been determined, but offers a unique opportunity to investigate the interactions between these two important tissues. One of the genes which causes albinism encodes for an orphan GPCR (OA1) expressed only in pigmented cells, including the RPE.

[0063] **Methodology/Principle Findings:** The function and signaling of OA1 was investigated in RPE and transfected cell lines. The results indicate that OA1 is a selective L-DOPA receptor, with no measurable second messenger activity from two closely related compounds, tyrosine and dopamine. Radiolabeled ligand binding confirmed that OA1 exhibited a single, saturable binding site for L-DOPA. Dopamine competed with L-DOPA for the single OA1 binding site suggesting it could function as an OA1 antagonist. OA1 response to L-DOPA was defined by several common measures of GPCR activation including influx of intracellular calcium and recruitment of β-arrestin. Further, inhibition of tyrosinase, the enzyme that makes L-DOPA, resulted in decreased PEDF secretion by RPE. Further, stimulation of OA1 in RPE with L-DOPA resulted in increased PEDF secretion.

[0064] **Conclusions/Significance:** Taken together the results illustrate an autocrine loop between OA1 and tyrosinase linked through L-DOPA, and this loop includes the secretion of at least one very potent retinal neurotrophic factor. OA1 is a selective L-DOPA receptor whose downstream effects govern spatial patterning of the developing retina. The results suggest that the retinal consequences of albinism caused by changes in melanin synthetic machinery may be treated by L-DOPA supplementation.

[0065] **Introduction:** Albinism is a group of inherited genetic diseases in which there is a variable loss of pigmentation in the eye, hair or skin. When the eye is affected, there are significant alterations in neurosensory retina development that lead to low vision [1-8]. There are two broad classes of albinism, ocular-cutaneous albinism (OCA) and ocular albinism (OA). OCA occurs when all pigmented tissues exhibit hypopigmentation and involves genetic mutations that result in defects in the melanin synthetic machinery [3,7-9]. OA occurs when cutaneous tissues pigment normally, but the ocular tissues are hypopigmented [10,11]. Since the same proteins produce pigment in all tissues, OA most likely

results from lack of expression of the melanogenic enzymes in ocular tissue rather than an inability to synthesize melanin because the other tissues pigment normally.

[0066] OA can be linked to at least one gene, *Oa1,* which is found on the X chromosome. *Oa1* encodes a 404 amino acid protein likely to be an orphan G-protein coupled receptor (GPCR), OA1 (Genbank GPR143) [12,13] based upon sequence analysis [14]. Schiaffino *et al.* has demonstrated that OA1 associates with several G_{α} subunits as well as G_{β} adding further evidence that OA1 is a GPCR [14,15]. Indeed, Innamorati *et. al.* used a combinatorial expression strategy to illustrate GPCR-like activity from OA1, as well as β-arrestin association, even in the absence of a ligand [16]. This work suggested that OA1 could signal through a Gαq subunit through phospholipase C and inositol triphosphate second messengers. In a yeast based expression system, Staleva and Orlow have demonstrated GPCR signaling from OA1 that appeared to be activated by a component in the melanosomal compartment [17]. Despite the significant amount of circumstantial evidence that OA1 is a GPCR, confirmation is lacking because no ligand has been identified. Other data has called into question the idea that OA1 is a GPCR. For example, the localization of OA1 as a fully intracellular protein is not typical of GPCRs and suggests that it would be a unique member of the family [14]. OA1 is primarily localized to the endolysomal compartment [14,15,18-21] and melanosomes [11,14,22] rather than the cell surface.

[0067] In this study the function of OA1 as a potential GPCR was investigated, based on the hypothesis that the endosomal localization of OA1 in cultured cells was due to internalization of OA1 in response to an agent in the culture medium. Further, a ligand for OA1 was sought based on the observation that all forms OCA and OA appear to have the same retinal phenotype, indicating that tyrosinase activity and OA1 signaling are coupled upstream of retinal development. Thus, tests on whether tyrosinase activity produces the ligand for OA1 were carried out. A by-product of melanin synthesis is L-DOPA, which is released to the retina during melanin synthesis in the RPE at a critical time in retinal development [23,24]. The data suggest that OA1 is a highly selective L-DOPA receptor, and that L-DOPA causes OA1 signaling with the downstream effect of neurotrophic factor secretion by RPE. Thus, the first evidence is presented of a ligand for OA1, and provide a mechanism through which either tyrosinase or OA1 deficiency results in changes to retinal development.

Results:

Cell Surface Localization of OA1.

[0068] OA1 has previously been localized in pigment granules *in situ* [22], however, using transfected cells of various types, OA1 also has been localized to both the plasma membrane [16,17] and the endosomal fraction of cultured cells [14,16-18,20,21]. The investigation began by determining where OA1 resides in the human tissue using cell surface biotinylation/westem blot strategies. In the human eye, OA1 was present on the apical cell surface of the RPE *in situ* (Fig. 1 A). Quantification of cell surface, biotinylated OA1 in five human eyes indicated that at least 3.5 +/- .7% of the total OA1 resided on the apical cell surface of RPE *in situ.* Access to the biotinylation reagent using eye cup preparations is restricted to the apical surface, so the polarity of OA1 in the epithelium cannot be determined. Further, the total cell surface OA1 is likely underestimated because of the lack of access to the basal cell surface. Blots were also probed with antibodies against actin as a control to verify that cytoplasmic proteins were not biotinylated. In each experiment actin was only found in the unbound fraction.

[0069] Others have reported that recombinant OA1 and OA1-GFP is almost exclusively localized to the endosomal compartment in cultured cells [14,15,17,18,20-22]. However, when overexpressed [16], or when endocytosis is inhibited [17], OA1 accumulates at the cell surface. The observation that OA1 protein is present on the apical surface of RPE *in situ* led us to explore the issue further.

Effects of Tyrosine on OA1 Expression and Distribution

[0070] Endosomal localization of GPCRs occurs normally after exposure to a ligand. Therefore, it was investigated whether a ligand for the receptor was present in the standard incubation medium that could drive internalization of OA1. Since the standard culture medium contains 500 μM tyrosine, and tyrosine is the starting material for pigment synthesis, the effect of tyrosine on receptor distribution was evaluated. To test whether tyrosine affected OA1 distribution in cultured cells DMEM was formulated without tyrosine, and dialyzed fetal bovine serum was used. In the presence of tyrosine-free medium, OA1 was detected on the plasma membrane of cultured RPE cells both in the absence (not shown), and in medium containing low concentrations of tyrosine (1 μM, Fig. 1 B). Averaged over five experiments, 4.5 +/- 1% of total OA1 protein was observed on the surface of cultured RPE maintained in 1 μM tyrosine, similar to what was observed for RPE *in situ*. In all experiments actin was observed in the unbound protein fraction, demonstrating the absence of any cytoplasmic protein in the cell surface assay. Similarly, OA1-GFP expressed in COS illustrated a cell surface expression that was tyrosine sensitive (Fig. 1 C). Quantification of six such experiments indicated significant variability in the amount of OA1 found at the cell surface using transient transfections. The range of OA1 in the bound fraction of transfected cells maintained in 1 μM tyrosine ranged between 5-40%, unlike the results with the endogenous OA1 protein

that were reproducibly ~5%.

[0071] Not only was the distribution of OA1 in transfected cells sensitive to tyrosine levels in the medium, total OA1-GFP expression was increased 5-fold in cells maintained in 1 μM tyrosine. To verify that this difference related to OA1 expression rather than cell number, actin expression was evaluated from the paired samples. The data (Fig. 1 D) presented as optical density units indicate no difference in actin. The amount of cell surface OA1 between the normal and low tyrosine groups was also compared. Importantly, in the five RPE experiments and six OA1-GFP in COS experiments, OA1 in the plasma membrane fraction of cells in standard medium was not reproducibly detected, similar to that found by others.

[0072] The distribution of OA1 in RPE cells also was evaluated by confocal microscopy. OA1 has previously been characterized as an endosomal protein in cultured RPE cells as shown in (Fig. 1 E). In contrast, the distribution of OA1 in low tyrosine medium was diffuse on the plasma membrane of cultured RPE cells, with little endosomal accumulation (Fig. 1 F), an observation consistent with the results obtained using biochemical methods.

L-DOPA as a Natural Agonist for OA1.

[0073] Tyrosinase function in melanogenesis begins with its activity on tyrosine to create L-DOPA, followed by a second reaction to create dopaquinone that leads to pigment formation [25]. Of the intermediates between tyrosine and melanin, L-DOPA has the greatest half-life, and L-DOPA is released into the subretinal space apical to the RPE when melanin synthesis occurs [23,24]. L-DOPA is also the precursor to dopamine, a neurotransmitter produced by dopaneurgic neurons from tyrosine. The release of calcium from intracellular stores is a common downstream effect of GPCR activation by a ligand. Since the expression of OA1 on the cell surface appears to be sensitive to tyrosine, it was examined whether tyrosine, or its metabolites L-DOPA and dopamine, could stimulate influx of Ca^{2+} into the cytoplasm in an OA1-dependent manner. CHO cells were transfected with an OA1 expression vector then maintained in DMEM containing 1 μM tyrosine for 48 hours followed by tyrosine-free DMEM for 24 hours to facilitate cell surface expression of OA1. Intracellular Ca^{2+} was evaluated using Fura-2, and $[Ca^{2+}]i$ was determined by ratiometric imaging [26]. In the absence of any ligand, $[Ca^{2+}]i$ was not significantly different between transfected and untransfected cells (Fig 2). Tyrosine and several tyrosine metabolites were tested at 1 μM for an effect on $[Ca^{2+}]i$. As a positive control each experiment was ended by treatment with 20 mM KCl to depolarize the cell and increase $[Ca^{2+}]i$ via activation of voltage-gated channels. This maneuver served to verify the Fura-2 loading and responsiveness of the cells being tested (Fig. 2). Only L-DOPA elicited a significant increase in $[Ca^{2+}]i$ (Fig. 2 A). Tyrosine and dopamine had no positive effect on intracellular at $[Ca^{2+}]i$ concentrations up to 1 mM (not shown). The slight negative effect of 1 μM dopamine was not statistically significant, but reproducible among the 11 experiments with dopamine (Fig. 2 B).

[0074] Over expression of GPCRs in non-native cell lines can lead to false signal transduction coupling. To verify that OA1 signaling in response to L-DOPA was indeed a natural response, OA1 was expressed in RPE cells (Fig. 2 C). Results using transfected RPE cells were similar to those achieved with transfected CHO cells. RPE cells transfected to express OA1 responded to 1.0 μM L-DOPA with an increase in $[Ca^{2+}]i$. It was next determined whether RPE cells expressing the endogenous OA1 receptor, at endogenous levels exhibited L-DOPA responsiveness. Like all of the transfected cell experiments, RPE expressing OA1 demonstrated an increase in $[Ca^{2+}]i$ after treatment with 1.0 μM L-DOPA (Fig. 2 C).

[0075] To further characterize OA1 signaling activity, pertussis toxin was used to distinguish between Gq coupled $[Ca^{2+}]i$ signaling and G_i linked signaling (Fig. 2 C). In all cells studied, pertussis toxin lowered the basal level of $[Ca^{2+}]i$, indicating its activity on inhibition of the background signaling through G_i subunit activity. Pertussis toxin was used in experiments conducted in cells transfected to express OA1 including both CHO and RPE, as well as RPE expressing the endogenous OA1 protein at natural levels. In all transfected cells tested the measured $[Ca^{2+}]i$ response to L-DOPA was greater than in the absence of the toxin (Fig 2), owing largely to the lower initial $[Ca^{2+}]i$. Thus, the signaling through OA1 in response to L-DOPA that results in increase $[Ca^{2+}]i$ is not pertussis toxin sensitive and likely Gq subunit mediated. The second messenger cAMP was also measured in CHO cells transfected to express OA1 (Fig. 2 D). Using inactive cells or a submaximal forskolin treatment, the experiments were set up to measure either an increase or decrease in cAMP in response to L-DOPA. In six such experiments, no change in cAMP was observed suggesting neither G_s nor G_i subunits are involved in OA1 signaling.

[0076] Standard methods of radiolabeled ligand binding were used to characterize the interaction between OA1 and L-DOPA (Fig. 3 A). CHO cells were transfected to express OA1, then binding of L-DOPA was quantified in a concentration-dependent manner, and the results were further characterized by Scatchard Plot analysis (Fig. 3E). Results illustrate saturable binding of L-DOPA to OA1 expressing cells with a Kd of 9.35×10^{-6}M. No specific binding was observed in untransfected CHO cells, indicating that the cells do not have an endogenous L-DOPA receptor (not shown). All binding parameters, total, specific, and nonspecific are shown as supplemerital data (Figure 6A). Tyrosine exhibited the potential to interact with OCA1, but neither tyrosine nor dopamine stimulated OA1 signaling (see Fig. 2). Competitive ligand binding was used to determine whether either tyrosine or dopamine competed with L-DOPA for OA1 binding. At high

concentrations (1 mM), both tyrosine and dopamine competed with L-DOPA for OA1 binding (Fig. 3B). To further characterize this the kinetics of the competition between L-DOPA and either dopamine (Figure 3 C) or tyrosine (Fig. 6B) was examined. Dopamine exhibited competitive binding to a single site with L-DOPA with a Ki of 2.33 x 10 -6 +/- 0.2 x 10^{-6} M. Similar experiments with tyrosine demonstrated inhibition of L-DOPA binding only at high concentrations (Fig. 6B). Saturation kinetics were not possible with tyrosine because of its low affinity and insolubility at the high concentrations.

[0077] Given the relatively low affinity of OA1 for L-DOPA it was determined whether its signaling activity was dose-dependent in the range of this binding affinity. The concentrations in which binding data suggested the steepest rise in association between L-DOPA and OA1, 1.0 - 10 μM were tested, and results illustrate a concentration dependent GPCR response as measured by $[Ca^{2+}]i$ (Fig. 3 C). Thus, the activation kinetics of L-DOPA and OA1 matched the concentration range observed in radiolabeled ligand binding experiments.

[0078] In response to ligand binding, GPCRs recruit β-arrestin to the plasma membrane which is followed by internalization of the ligand-receptor complex [27-33]. The effect of L-DOPA on β-arrestin localization was then tested (Fig. 4). Cells were transfected to express OA1 then cultured in 1 μM tyrosine DMEM for 48 hours prior to analysis to allow cell surface expression of the protein. Cells were then treated with 1 μM L-DOPA followed by rapid fixation on ice in cold methanol. Initially, under resting conditions in the absence of an agonist, OA1-GFP was found at the cell surface and β-arrestin was diffuse in the cytoplasm (Fig. 4 A-C), with no co-localization between the proteins. After stimulation with L-DOPA, OA1 and β-arrestin were co-localized at the plasma membrane (Fig. 4 D-F). Untransfected cells showed no response to L-DOPA treatment (Fig. 4 G,H), illustrating that the L-DOPA effect on β-arrestin distribution was OA1 dependent, similar to results obtained for $[Ca^{2+}]i$.

Effects of 1-DOPA on PEDF Secretion

[0079] Mutations in OA1 cause defects in the development of the neurosensory retina. In previous work it has been shown that pigmented RPE secrete significantly more PEDF than nonpigmented RPE [34], and PEDF is a neurotrophic factor with the potential of altering neurosensory retina development [35-41]. Mutations in OA1 cause a loss of pigmentation in the RPE, suggesting that OA1 activity governs RPE pigmentation. Thus, it was determined whether L-DOPA stimulation of pigmented RPE cells caused increased secretion of PEDF (Fig. 5). This assay is made somewhat more difficult because pigmenting RPE cells produce L-DOPA, which is the agonist for OA1, and OA1 is not readily detectable in nonpigmented cultures of RPE. Thus, pigmented RPE were used to determine whether L-DOPA stimulation increases PEDF expression/secretion. RPE cells were placed in tyrosine-free medium for 24 hours then treated with 1 μM L-DOPA for one hour. After treatment, the cells were returned to standard medium without exogenous L-DOPA for three days. Control cells were not treated with L-DOPA, but the medium was changed at the same time the experimental cells were returned to normal medium. Conditioned medium was collected after three days and PEDF was measured. Results illustrate a significant increase in the secretion of PEDF in pigmented cells treated with L-DOPA when compared to paired, control monolayers of pigmented RPE (Fig. 5 A). Importantly, this significant increase occurred in cells which were pigmenting and therefore expressed OA1 and had a basal level of PEDF expression.

[0080] To determine whether pigmented RPE cells secrete PEDF through an autocrine loop involving tyrosinase activity and OA1 signaling, a specific tyrosinase inhibitor phenylthiourea (PTU) was used to inhibit pigmentation and L-DOPA production (Fig. 5B). In these experiments, pigmented RPE cells were either maintained in DMEM, or DMEM containing 200 μM PTU for three days, then PEDF secretion was measured. Pigmented RPE secreted substantial PEDF, but PTU caused a significant decrease in PEDF secretion indicating that tyrosinase activity is necessary for the high level of PEDF secretion observed in pigmented RPE cells. To verify that it was the lack of L-DOPA in the PTU treated cells that caused the decreased PEDF secretion, 3 different cultures of pigmented RPE were used, and exposed to PTU for 48 hours, then treated with 1.0 μM L-DOPA in the continued presence of PTU; PEDF was measured after 72 hours (Fig. 5 C). The data are presented as percent of control for this experiment because the cultures used varied in both pigmentation and PEDF expression before the experiment began. PTU treated RPE responded to the added L-DOPA by increasing PEDF secretion, indicating that the effect of PTU on PEDF secretion is caused be the lack of L-DOPA production when tyrosinase is inhibited.

Discussion:

[0081] There is a complex inter-tissue relationship between the RPE and the neurosensory retina. One aspect of this relationship is centered on RPE pigmentation, and defects in melanin synthesis which result in significant neurosensory retina alterations [8,23,42]. The data suggest that OA1 and tyrosinase participate in an autocrine loop through L-DOPA that regulates the secretion of at least one potent neurotrophic factor, PEDF. The data also suggest that the pathologic changes in retinal development that occur in albinism may result from changes in the activity of the OA1 signaling pathway. Reduced OA1 signaling activity can be caused either directly through OA1 mutations or indirectly through changes in L-DOPA production by tyrosinase activity. Thus, it is hypothesized that the similar retinal phenotypes that

accompany the diverse forms of albinism can be reconciled to a single common pathway, OA1 signaling.

[0082] In the study, OA1 on the apical surface of human RPE *in situ* was observed. Previous reports have suggested that OA1 in mice is localized to the melanosome [22], and in cultured cells to the endosomal compartment [15-18,20-22,43]. The results from *in situ* RPE preparations indicate that OA1 is distributed to the apical surface of the RPE. The limited quantities of OA1 on the surface of the RPE (~3.5% of total OA1) may account for the lack of observation of the protein in previous studies where immunogold electron microscopy was used. Like many cell surface GPCRs, OA1 is not an abundant protein.

[0083] The endosomal localization of OA1 reported in previous studies using cultured cells was reproduced in this study for both the endogenous protein and the transgenic protein. When tested in normal culture medium little detectable OA1 protein on the cell surface was found, in agreement with all previous work. However, reduction of tyrosine in the medium caused a modest increase in cell surface receptor accumulation of both the endogenous and recombinant OA1 proteins. This suggests that the distribution of OA1 to the cell surface in cultured cells is sensitive to tyrosine. A previous study has demonstrated OA1 could be localized to the cell surface when endocytosis in inhibited [17] and OA1 on the apical surface of human RPE was observed *in situ*. The data suggest OA1 is a cell surface GPCR, but is a target for endocytosis that may be stimulated by tyrosine or tyrosine metabolites. In this regard, the results differ from past reports of OA1 localization that have classified OA1 as a unique type of intracellular GPCR. Most GPCRs are cell surface proteins that are internalized by a variety of signals, and the data suggest OA1 is similar to most other GPCRs.

[0084] OA1 signaling activity was stimulated by L-DOPA, but not by either its precursor, tyrosine, or its neuronal metabolite dopamine. This result suggests an exquisitely sensitive receptor activity able to distinguish between closely related molecules, after all L-DOPA and tyrosine differ by a sole hydroxyl group. OA1 is sensitive to tyrosine, as tyrosine causes an intracellular localization of OA1 in cultured cells. However, no signaling response to tyrosine was noted, and competition binding studies suggest that tyrosine has a low affinity for OA1. The data suggest that the continuous exposure of cells to high concentrations of tyrosine present in normal medium is sufficient to result in internalization of OA1, but it is unlikely to result in measurable OA1 activation. Strong evidence of a single site competitive interaction between L-DOPA and dopamine was found. The Ki observed for dopamine was similar to the Kd observed for L-DOPA, suggesting that the affinity for the two tyrosine metabolites is similar. The results illustrated a slight, but reproducible, decrease in OA1 signaling from dopamine, suggesting that dopamine may be an effective antagonist or inverse agonist for OA1.

[0085] As an orphan GPCR, its signaling pathway has not previously been identified. In this study it was illustrated that OA1 signaling in response to L-DOPA causes an increase in $[Ca^{2+}]i$. The data illustrate that the increased $[Ca^{2+}]i$ observed in response to L-DOPA was insensitive to pertussis toxin and no effects on cAMP were found, indicating that OA1 is likely signaling through a Gq subunit. Previous work has suggested that OA1 can associate with multiple subunits in transfected cells including members of the G_o, G_i, and Gq subunit families. Innamorati *et al.* has shown that spontaneous activity of overexpressed OA1 is likely signaled through a Gq subunit [16]. The data indicate that ligand-dependent signaling from endogenous OA1 in RPE most likely occurs through a Gq mediated pathway, and no promiscuous coupling activities were observed when comparing OA1 over expression in CHO and RPE to natural OA1 expressed in RPE. Interestingly, two overactive mutant forms of Gq subunits cause hyperpigmentation in skin and hair [44], but whether they have an effect in RPE is unknown. RPE and cutaneous melanocytes use the same enzymes to produce pigmentation but differ in their control of melanogenesis. A recent report suggests that OA1 may signal through $G\alpha i3$, because the retinal phenotype of OA1 $^{-/-}$ and $G\alpha i3^{-/-}$ are similar [45]. That study provided no data regarding interaction or signaling between $G\alpha i3$ and OA1, and the results do not support OA1 signaling through $G\alpha i3$. However, both OA1 and $G\alpha i3$ could have activity in convergent pathways that govern some part of the complex system of retinal development.

[0086] The response of OA1 to L-DOPA was measured in three ways, increased $[Ca^{2+}]i$, recruitment of β-arrestin to plasma membrane OA1, and the increased secretion of PEDF. In addition, inhibiting the activity of tyrosinase in pigmented RPE inhibits L-DOPA production, and results in a decreased secretion of PEDF. Taken together, these studies present a strong argument for a productive ligand:receptor relationship between L-DOPA and OA1. Further, the data suggest selectivity among tyrosine and its metabolites, with only L-DOPA being a productive ligand for OA1. We have determined the binding kinetics between OA1 and L-DOPA, and observed a typical one site receptor:ligand relationship between the two. The binding affinity between OA1 and L-DOPA, with a Kd in the μM range, is not uncommon for an endogenous ligand:receptor relationship. Future identification of a specific, high affinity antagonist for OA1 will aid in further biochemical characterization of the interaction between OA1 and L-DOPA, and be useful in determining whether dopamine is an inverse agonist.

[0087] This study illustrated the selective activation of OA1, an orphan GPCR, by L-DOPA, an intermediate product of melanin synthesis. This study has also illustrated that OA1 activity stimulates PEDF secretion by RPE, a molecule that has the potential to support normal retinal development [40,41]. In humans, this suggests that pharmacologic intervention through OA1 activation could be useful for albinism caused by defects in the melanogenic machinery (OCA 1-4). Unfortunately, the data also suggest that OA1 is necessary for such pharmacologic intervention, and mutations in *Oa1* are the most common cause of albinism.

Methods:

Cell Culture

[0088] **RPE-** Cells were isolated as described [46] and maintained in Dulbecco's modified essential medium (DMEM) supplemented with 5% fetal bovine serum (FBS). For experiments in which tyrosine concentrations were lowered, custom manufactured DMEM produced without tyrosine by JRH Biosciences (Lenexa, KS) was used. Dialyzed FBS was purchased from Invitrogen, (San Diego, CA).

[0089] **COS-7** and **CHO-** Cells were obtained from ATCC and cultured in DMEM supplemented with 5% FBS. For analysis of OA1 distribution, cells were cultured in tyrosine-free DMEM supplemented with 1 μM tyrosine, 5% dialyzed FBS for 2-4 days, then tyrosine-free media as described for the experiment.

Cell Surface Biotinylation

[0090] **Human *RPE in situ-*** Human eyecups were produced by dissection ~2mm anterior to the equator and removals of the anterior segment. The vitreous and retina were removed without impairing the underlying RPE monolayer, and the retina was cut at the optic nerve head. The resulting eyecups with RPE exposed were rinsed three times with reaction buffer (100 mM NaCl, 50 mM NaHCO3, pH 8.0) then filled with Sulfo-NHS-LC-Biotin (1 mg/ml) two times for thirty minutes. The reaction was stopped with TG buffer (25 mM Tris, 192 mM Glycine, pH 8.3) then the cells were harvested in lysis buffer (2 mM EDTA, 1% Triton X and 1% Tween 20 in Tris Base Saline Buffer) containing Halt Protease Inhibitor Cocktail. Intact cells and pigment granules were removed by centrifugation at 14,000 rpm for 20 minutes. Biotinylated proteins were captured overnight with immobilized streptavidin beads and then mixed with 4X reducing buffer (250 mM Ttis, pH 6.8, 8% SDS, 40% Glycerol, 20% Beta-mercaptoethanol, 0.08% bromophenol blue). The OA1 protein was separated on a 10% SDS-PAGE gel and identified by a using a polyclonal rabbit OA1 antibody for western blot analysis. Paired western blots were probed with a monoclonal antibody directed against actin.

[0091] **Cultured Cells-** RPE and transfected cells were maintained in DMEM containing tyrosine concentrations described for the experiments. Cultures were rinsed three times in reaction buffer, then biotinylated as described above for *the in situ* preparation.

Cloning of *Oa1*

[0092] A cDNA library was constructed from pooled tissue from 6 human donor eyes. Total RNA was harvested using Trizol reagent, then cDNA was synthesized using Poly-T primers for the first strand synthesis, and random hexamers for the second strand. Following cDNA synthesis, RNA was removed using RNase A. The coding sequence for OA1 was obtained by PCR using terminal primers that added restriction sites to the 5' and 3' ends and removed the native stop codon. The PCR product was ligated in frame with GFP in the pEGFP N-1 vector (Clontech). The sequence was verified by automated sequencing in both directions over the entire sequence.

Immunocytochemistry

[0093] Cells on slides were fixed with 3% paraformaldehyde at RT, rinsed with 0.1% Triton X-100 in 10% milk in TBST then blocked with 10% milk in TBST. β-arrestin was visualized using a polyclonal antibody directed against β-arrestin, and incubated overnight at 4°C. Cover slips were mounted using 50% glycerol and immunostaining was analyzed by optical sectioning using a Nikon Eclipse E800 laser scanning confocal microscope powered by Compix Confocal Imaging Systems software (Simple PCI Version 4.0.6.1605). Three-dimensional analysis of OA1-GFP and β-arrestin distribution was performed in Image J 1.32.

Measurement of $[Ca^{2+}]i$

[0094] OA1-GFP expressing CHO cells plated on glass cover slips were rinsed in Ca^{2+} containing HEPES buffered Hanks Balanced Salt Solution (HBSS) (pH 7.45), then incubated with 2.5 μM Fura-2 (solubilized in anhydrous dimethylsulfoxide and 0.002% pluronic acid) for 20 minutes at 37°C, 5% CO_2.The Fura-2 loaded cells were rinsed with HBSS for 15 minutes at 37°C, 5% CO_2 to allow for full cleavage of the dye to its active form. Each cover slip was incubated in 1 ml of HBSS in a chamber held at 37°C on the stage of an inverted Olympus IX70 microscope equipped with a 40 x 1.35 NA UV-fluor objective.

[0095] Using a filter wheel, excitation light from a 200 W Xe bulb was passed alternately through 340 and 380 nm filters. A 10 nm bandpass filter, centered at 510 nm, selected for the emitted fluorescence which was passed to a CCD camera (Photometrics CH-250). For each experiment, image pairs were taken every minute for the first three minutes,

which established a stable baseline. Then L-DOPA (1 μM final concentration) was added and image sets were taken every 30 seconds for the next three minutes. Finally, KCl (20 mM final concentration) was added one minute before completion of each experiment as a positive control to establish that the cells were loaded with Fura-2. The same was repeated independently for tyrosine and dopamine (both at 1 μM final concentration). Using a Silicon Graphics Personal IRIS computer, the 340/380 nm ratio was computed for each pixel within a cell, and then analyzed using Microsoft Excel version 4.0 (Microsoft, Redmond, WA). Once the 340/380 nm ratio was determined, each ratio was normalized to 1 (ratio at time zero divided by itself), then the free ion concentration was calculated using the following equation:

$$[Ca_i]\# = Kd\# * (R - R_{min}\#)/R_{max}\# - R)$$

in which R, R_{min}, and R_{max} are the measured, minimum, and maximum ratios, respectively. R_{max} represents the ratio of fluorescence intensity of ion-sensitive wavelengths under fully deprotonated conditions, whereas R_{min} is the ratio for the dye when it is fully protonated. In the case of Fura-2, R increases with increasing Ca^{2+}; hence R_{min} represents Fura-2 in the absence of Ca^{2+} (Ca^{2+} <1 nM) whereas R_{max} represents the Ca^{2+}-Fura-2 chelate as previously described [26]. R_{min}, R^{max} and Kd were determined in independent experiments in Fura-2 loaded cells, and subsequently utilized for calculation of free Ca^{2+} for the experimental procedures.

Radiolabeled Ligand Binding

[0096] CHO cells were transfected to express OA1-GFP were plated into 24-well plates. Cells were chilled to -2C, then rinsed in cold binding buffer, 25 mM Tris, 150 mM NaCl, 5 mM EDTA, 5 μM digitonin (pH 7.45). Cells were incubated for two hours in binding buffer containing [^{3}H]-L-DOPA (Moravek Biochemicals, Brea, CA) at concentrations between 10^{-4}M to 10^{-9}M. The temperature was not allowed to exceed -2°C at any step of the assay. Controls included assays conducted on nontransfected CHO and specific binding was determined by competition with excess unlabelled L-DOPA at 10^{-3}M. Bound L-DOPA was quantified by scintillation spectroscopy.

Measurement of cAMP

[0097] Cells were pretreated with forskolin (15 minutes) then challenged with L-DOPA using an assay setup as previously described [47]. After 1 minute of ligand exposure, cells are scraped into ice-cold buffer, boiled then centrifuged. Equivalent volumes, 50 μl, of supernate and ^{3}H-cAMP (New England Nuclear) then combined with 100 μl cold PKA. After 2 hours, the solution is passed over activated charcoal, and supernates are counted in a scintillation counter. Results are compared to those achieved using a standard curve, instead of cytosol, produced using 50 μl of cAMP 0.25-32.0 pmole/50μl.

Example 2: The OA1 loop functions in vivo

[0098] PEDF secretion in OA deficient mice was compared to wild type mice, and showed that wild-type mice secreted significantly more PEDF than OA1-/y mice. The culture medium (C.M.) used contains PEDF, and it is likely that PEDF in the CM from OA1 -/y is from the medium used, not the RPE. Results (Figure 7) are quantified and summarized in the graph. The difference, even with the background PEDF in the CM for both groups is significant. T-test analysis results are presented

[0099] Tyrosinase deficient pregnant mice were maintained under normal conditions (No L-DOPA), or supplemented with 1.0mg/ml L-DOPA in there drinking water, beginning on embryonic day 7 for their pups. Animals were maintained on supplemental until postnatal day 14, when ocular development is over and the eyes are open.

[0100] Two cell types are reduced in number in albinism: retinal ganglion cells and photoreceptors. Figure 8A demonstrates that L-DOPA supplementation increases retinal ganglion cell numbers compared to what is expected in a normal wild-type mouse. Figure 8B shows the same result for photoreceptors. Photoreceptors are not counted directly as they are too dense. Rather, the area occupied by photoreceptor nuclei is measured as a measure of photoreceptor numbers. L-DOPA supplementation increased the photoreceptor nuclear area, so the number of photoreceptors were increased. Again, this appeared to restore the albino animal to normal levels.

[0101] As shown in Figure 8C, Four paired littermate animals, 2 wild-type and 2 OA1 -/y (female OA1 deficient) were euthanized and the retinas from each animal were loaded independently in a lane, then proteins were western blotted to detect PEDF, which was readily observed in the retina from wild-type mice. In contrast, PEDF is not readily detected in the retinas from the OA1 -/y mice.

[0102] In summary this data illustrate that OA1 -/y mice make less PEDF than wild type mice. L-DOPA stimulation in

tyrosinase defective mice rescues the two most prominent neurosensory retina defects of albinism: a loss of photoreceptor cells and retinal ganglion cells. Finally, PEDF levels are reduced in the retinas of mice lacking OA 1. Thus, it is concluded that the OA1 autocrine loop functions in vivo, and can be stimulated with oral L-DOPA.

[0103] The data together illustrate that the linkage between RPE pigmentation and AMD are likely through the signaling activity of OA1. The data illustrate that the ligand for OA1 is L-DOPA, and that OA1 signaling from L-DOPA controls the expression of PEDF. PEDF is the most potent neurotrophic factor made by RPE. Thus, the identification of L-DOPA as the ligand for OA1, which controls PEDF expression, ties together L-DOPA and neurotrophic activity in the RPE. Because L-DOPA is produced as a by-product of pigment production, this established for the first time a linkage between RPE pigmentation and neurotrophic activity. This system is defined as the OA1 autocrine loop. Tyrosinase makes pigment and releases L-DOPA. Released L-DOPA binds to and initiates signaling through OA1. OA1 signaling controls the expression of both tyrosinase and PEDF.

[0104] To date the data illustrate this model biochemically, in cultured cells, and *in vivo.* The fact that retinal development in an albino animal can be rescued using dietary L-DOPA indicates that dietary L-DOPA can be used to stimulate RPE trophic factor expression *in vivo.* AMD is clearly tied to an RPE defect somehow related to its pigmentation. Blue-eyed individuals get AMD at a much greater frequency than dark-eyed individuals, so the level of RPE pigmentation controls the AMD process. The level of RPE pigmentation is controlled by OA1 signaling and is part of the same OA1 autocrine loop described above. Thus, AMD is related to OA1 signaling in RPE. Therefore, those with lower RPE pigmentation will have lower tyrosinase, lower L-DOPA, lower OA1 signaling, and lower PEDF production. We can use dietary L-DOPA as ligands for OA1 and stimulate that activity. The final determinant of the health of the neurosensory retina is PEDF, but we can use OA1 signaling to increase the OA1 loop activity, and increase the neurotrophic activity of the RPE. The effect of OA1 signaling will be to foster neuron survival.

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SEQUENCE LISTING

[0106]

SEQUENCE LISTING

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<210> 2
<211> 424
<212> PRT
<213> Homo sapiens

<400> 2

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1               5                  10                  15

Arg Thr Gln Pro Met Ala Ser Pro Arg Leu Gly Thr Phe Cys Cys Pro
            20                  25                  30

Thr Arg Asp Ala Ala Thr Gln Leu Val Leu Ser Phe Gln Pro Arg Ala
        35                  40                  45

Phe His Ala Leu Cys Leu Gly Ser Gly Gly Leu Arg Leu Ala Leu Gly
    50                  55                  60

Leu Leu Gln Leu Leu Pro Gly Arg Arg Pro Ala Gly Pro Gly Ser Pro
65                  70                  75                  80

Ala Thr Ser Pro Pro Ala Ser Val Arg Ile Leu Arg Ala Ala Ala Ala
                85                  90                  95

Cys Asp Leu Leu Gly Cys Leu Gly Met Val Ile Arg Ser Thr Val Trp
            100                 105                 110

Leu Gly Phe Pro Asn Phe Val Asp Ser Val Ser Asp Met Asn His Thr
        115                 120                 125

Glu Ile Trp Pro Ala Ala Phe Cys Val Gly Ser Ala Met Trp Ile Gln
    130                 135                 140

Leu Leu Tyr Ser Ala Cys Phe Trp Trp Leu Phe Cys Tyr Ala Val Asp
145                 150                 155                 160

Ala Tyr Leu Val Ile Arg Arg Ser Ala Gly Leu Ser Thr Ile Leu Leu
                165                 170                 175
```

```
Tyr His Ile Met Ala Trp Gly Leu Ala Thr Leu Leu Cys Val Glu Gly
            180                 185                 190

Ala Ala Met Leu Tyr Tyr Pro Ser Val Ser Arg Cys Glu Arg Gly Leu
        195                 200                 205

Asp His Ala Ile Pro His Tyr Val Thr Met Tyr Leu Pro Leu Leu Leu
    210                 215                 220

Val Leu Val Ala Asn Pro Ile Leu Phe Gln Lys Thr Val Thr Ala Val
225                 230                 235                 240

Ala Ser Leu Leu Lys Gly Arg Gln Gly Ile Tyr Thr Glu Asn Glu Arg
                245                 250                 255

Arg Met Gly Ala Val Ile Lys Ile Arg Phe Phe Lys Ile Met Leu Val
            260                 265                 270

Leu Ile Ile Cys Trp Leu Ser Asn Ile Ile Asn Glu Ser Leu Leu Phe
        275                 280                 285

Tyr Leu Glu Met Gln Thr Asp Ile Asn Gly Gly Ser Leu Lys Pro Val
    290                 295                 300

Arg Thr Ala Ala Lys Thr Thr Trp Phe Ile Met Gly Ile Leu Asn Pro
305                 310                 315                 320

Ala Gln Gly Phe Leu Leu Ser Leu Ala Phe Tyr Gly Trp Thr Gly Cys
                325                 330                 335

Ser Leu Gly Phe Gln Ser Pro Arg Lys Glu Ile Gln Trp Glu Ser Leu
            340                 345                 350

Thr Thr Ser Ala Ala Glu Gly Ala His Pro Ser Pro Leu Met Pro His
        355                 360                 365

Glu Asn Pro Ala Ser Gly Lys Val Ser Gln Val Gly Gly Gln Thr Ser
    370                 375                 380

Asp Glu Ala Leu Ser Met Leu Ser Glu Gly Ser Asp Ala Ser Thr Ile
385                 390                 395                 400

Glu Ile His Thr Ala Ser Glu Ser Cys Asn Lys Asn Glu Gly Asp Pro
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Ala Leu Pro Thr His Gly Asp Leu
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420

<210> 3
<211> 1651
<212> DNA
<213> Mus musculus

<400> 3

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<210> 4
<211> 405
<212> PRT
<213> Mus musculus

<400> 4

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Ala Thr Gln Leu Val Leu Ser Phe Gln Pro Arg Val Phe His Ala Leu
            20                  25                  30

Cys Leu Gly Ser Gly Thr Leu Arg Leu Val Leu Gly Leu Leu Gln Leu
        35                  40                  45

Leu Ser Gly Arg Arg Ser Val Gly His Arg Ala Pro Ala Thr Ser Pro
    50                  55                  60

Ala Ala Ser Val His Ile Leu Arg Ala Ala Thr Ala Cys Asp Leu Leu
65                  70                  75                  80

Gly Cys Leu Gly Ile Val Ile Arg Ser Thr Val Trp Ile Ala Tyr Pro
                85                  90                  95

Glu Phe Ile Glu Asn Ile Ser Asn Val Asn Ala Thr Asp Ile Trp Pro
            100                 105                 110

Ala Thr Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Leu Tyr Ser
        115                 120                 125

Ala Cys Phe Trp Trp Leu Phe Cys Tyr Ala Val Asp Val Tyr Leu Val
    130                 135                 140

Ile Arg Arg Ser Ala Gly Arg Ser Thr Ile Leu Leu Tyr His Ile Met
145                 150                 155                 160

Ala Trp Gly Leu Ala Val Leu Leu Cys Val Glu Gly Ala Val Met Leu
                165                 170                 175

Tyr Tyr Pro Ser Val Ser Arg Cys Glu Arg Gly Leu Asp His Ala Ile
            180                 185                 190

Pro His Tyr Val Thr Thr Tyr Leu Pro Leu Leu Leu Val Leu Val Ala
        195                 200                 205

Asn Pro Ile Leu Phe His Lys Thr Val Thr Ser Val Ala Ser Leu Leu
```

```
            210                 215                 220

Lys Gly Arg Lys Gly Val Tyr Thr Glu Asn Glu Arg Leu Met Gly Ala
225                 230                 235                 240

Val Ile Lys Thr Arg Phe Phe Lys Ile Met Leu Val Leu Ile Ala Cys
                245                 250                 255

Trp Leu Ser Asn Ile Ile Asn Glu Ser Leu Leu Phe Tyr Leu Glu Met
            260                 265                 270

Gln Pro Asp Ile His Gly Gly Ser Leu Lys Arg Ile Gln Asn Ala Ala
        275                 280                 285

Arg Thr Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Ala Gln Gly Leu
    290                 295                 300

Leu Leu Ser Leu Ala Phe Tyr Gly Trp Thr Gly Cys Ser Leu Asp Val
305                 310                 315                 320

His Pro Pro Lys Met Val Ile Gln Trp Glu Thr Met Thr Ala Ser Ala
                325                 330                 335

Ala Glu Gly Thr Tyr Gln Thr Pro Val Arg Ser Cys Val Pro His Gln
            340                 345                 350

Asn Pro Arg Lys Val Val Cys Val Gly Gly His Thr Ser Asp Glu Val
        355                 360                 365

Leu Ser Ile Leu Ser Glu Asp Ser Asp Ala Ser Thr Val Glu Ile His
    370                 375                 380

Thr Ala Thr Gly Ser Cys Asn Ile Lys Glu Val Asp Ser Ile Ser Gln
385                 390                 395                 400

Ala Gln Gly Glu Leu
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```

<210> 5
<211> 1723
<212> DNA
<213> Xenopus tropicalis

<400> 5

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aggtttcatt agtaatatgt cactaatgaa cacgtcagac atctggcctt caacttttg 420

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ttattatcct tccgtttcca attgtgaaaa cggactagaa catgcaatcc ctcattatgt 660

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gaatgttgat tttaatttca gacagaagga aacagcttgg gaacgagtgt ccacatctac 1080

aataactgaa actgcacaca atggcaccaa tggatctttc ctggattacc ctggctatat 1140

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<210> 6
<211> 400
<212> PRT

<213> Xenopus tropicalis

<400> 6

```
Met Ala Ser Pro Arg Leu Glu Thr Phe Cys Cys Pro Asn Arg Asp Pro
1               5                  10                  15
```

```
Ala Thr Gln Leu Val Leu Asp Phe Gln Pro Gln Ile Tyr Gly Ser Leu
            20                  25                  30

Cys Ile Gly Ser Gly Leu Val Ser Leu Leu Leu Thr Ile Val Gln Leu
        35                  40                  45

Leu Pro Lys Thr Lys Gln Gly Tyr Arg Arg Leu Gly Arg Ala Met Leu
    50                  55                  60

Pro Lys Pro Ser Ser Ser Arg Ile Leu Phe Leu Val Ile Ile Cys Asp
65                  70                  75                  80

Leu Leu Gly Cys Leu Gly Ile Leu Ile Arg Ser Ser Val Trp Ile Ser
                85                  90                  95

Ser Pro Gly Phe Ile Ser Asn Met Ser Leu Met Asn Thr Ser Asp Ile
            100                 105                 110

Trp Pro Ser Thr Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Phe
        115                 120                 125

Tyr Ser Ala Ser Phe Trp Trp Leu Phe Cys Tyr Ala Ile Asp Ala Tyr
    130                 135                 140

Leu Val Val Arg Arg Ser Ala Gly Ile Ser Thr Ile Val Leu Tyr His
145                 150                 155                 160

Met Met Thr Trp Gly Leu Ala Leu Met Leu Cys Ile Glu Gly Val Ala
                165                 170                 175

Met Leu Tyr Tyr Pro Ser Val Ser Asn Cys Glu Asn Gly Leu Glu His
            180                 185                 190

Ala Ile Pro His Tyr Val Thr Thr Tyr Ala Pro Leu Leu Ile Val Met
        195                 200                 205

Phe Ala Asn Pro Ile Leu Phe Arg Arg Thr Val Ala Ala Val Ala Ser
    210                 215                 220

Leu Leu Lys Gly Arg Gln Gly Ile Tyr Thr Glu Asn Glu Arg Arg Leu
225                 230                 235                 240

Gly Thr Glu Ile Gln Leu Arg Phe Phe Lys Ile Met Leu Val Phe Met
                245                 250                 255

Ile Cys Trp Thr Ala Asn Ile Ile Asn Glu Thr Leu Leu Phe Tyr Leu
            260                 265                 270
```

```
Glu Met Gln Pro Asp Ile Asn Thr Asp Gln Leu Lys Asn Val Arg Asn
        275                 280                 285

Ala Ala Leu Ile Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Met Gln
    290                 295                 300

Gly Phe Leu Phe Thr Leu Ala Phe Tyr Gly Trp Thr Gly Trp Asn Val
305                 310                 315                 320

Asp Phe Asn Phe Arg Gln Lys Glu Thr Ala Trp Glu Arg Val Ser Thr
                325                 330                 335

Ser Thr Ile Thr Glu Thr Ala His Asn Gly Thr Asn Gly Ser Phe Leu
            340                 345                 350

Asp Tyr Pro Gly Tyr Ile Gln Asn Gln Asn Lys Thr Glu Ile Gly Asn
        355                 360                 365

Ser Gln Gln Thr Asp Glu Ala Leu Ser Ile Leu Ser Glu Gly Asn Gly
    370                 375                 380

Ser Ile Val Glu Arg Leu Asn Arg Asn Ser Pro Ile Tyr Gln Gly Trp
385                 390                 395                 400
```

<210> 7
<211> 1585
<212> DNA
<213> Bos taurus

<400> 7

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tacatcacca cgtacttgcc gctgctactg gtcctggtgg gcaaccccat cctatttcga    660
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<210> 8
<211> 413
<212> PRT
<213> Bos taurus

<400> 8

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Met Ala Ser Pro Arg Leu Gly Thr Phe Cys Cys Pro Thr Arg Asp Ala
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Ala Thr Gln Leu Ala Leu Gly Phe Gln Pro Arg Ala Phe His Ala Leu
            20                  25                  30

Cys Leu Gly Ser Gly Ala Leu Arg Leu Ala Leu Gly Leu Leu Gln Leu
        35                  40                  45

Arg Pro Gly Arg Arg Pro Ala Gly Pro Gly Ile Ala Ser Ala Ser Pro
    50                  55                  60

Ala Thr Ser Ala Arg Val Pro Ala Ser Val Arg Ile Val Arg Ala Ala
65                  70                  75                  80

Thr Ala Cys Asp Leu Leu Gly Cys Leu Gly Ile Ala Val Arg Ser Ala
                85                  90                  95
```

```
Val Trp Leu Gly Phe Pro Ser Phe Val Asp Asp Ile Ser Ala Val Asn
            100                 105                 110

Asn Thr Asp Val Trp Pro Ala Val Phe Cys Val Gly Ser Ala Leu Trp
        115                 120                 125

Ile Gln Leu Leu Tyr Ser Ala Cys Phe Trp Trp Trp Phe Cys Tyr Ala
    130                 135                 140

Val Asp Ala Tyr Leu Val Ile Gln Arg Ser Ala Gly Gln Ser Thr Ile
145                 150                 155                 160

Leu Leu Tyr His Leu Met Thr Trp Gly Leu Ala Ala Leu Leu Ser Val
                165                 170                 175

Glu Gly Ala Leu Met Leu Tyr Tyr Pro Ser Met Ala Arg Cys Glu Arg
            180                 185                 190

Gly Leu Glu His Ala Ile Pro His Tyr Ile Thr Thr Tyr Leu Pro Leu
        195                 200                 205

Leu Leu Val Leu Val Gly Asn Pro Ile Leu Phe Arg Lys Thr Val Thr
    210                 215                 220

Ala Val Ala Ser Leu Leu Lys Gly Arg Gln Gly Ile Tyr Thr Glu Asn
225                 230                 235                 240

Glu Arg Arg Met Gly Ala Arg Ile Lys Thr Arg Phe Phe Lys Ile Met
                245                 250                 255

Leu Val Phe Ile Val Cys Trp Phe Ser Asn Val Ile Asn Glu Ser Leu
            260                 265                 270

Leu Phe Tyr Leu Glu Met Gln Pro Asp Ile Asn Ser Ser Ser Leu Lys
        275                 280                 285

Gln Val Arg Asn Ala Ala Lys Thr Thr Trp Phe Met Met Gly Ile Leu
    290                 295                 300

Asn Pro Ala Gln Gly Phe Leu Leu Ser Leu Ala Phe Tyr Gly Trp Thr
305                 310                 315                 320

Gly Cys Arg Leu Thr Leu Pro Gly Pro Ser Lys Glu Ile Gln Trp Asp
                325                 330                 335

Ser Met Thr Thr Ser Ala Thr Glu Gly Ala Pro Pro Ser Pro Gly Gly
            340                 345                 350
```

```
Pro Gln Glu Pro Gly Glu Gly Pro Ala Pro Lys Lys Glu Leu Pro Gly
        355                 360                 365

Gly Thr His Thr Ser Asp Glu Ala Leu Ser Leu Leu Ser Glu Gly Ser
    370                 375                 380

Gly Gly Ser Thr Ile Glu Ile His Ile Ala Ser Gly Ser Arg Gly Gly
385                 390                 395                 400

Lys Ala Pro Asp Ser Leu Pro Lys Val Gln Gly Thr Pro
                405                 410
```

<210> 9
<211> 1612
<212> DNA
<213> Rattus norvegicus

<400> 9

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ctccgcctgg tgcttggcct ccttcagctc ctaacagggc gccgatctgt tggtcacagg 240

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<210> 10
<211> 405
<212> PRT
<213> Rattus norvegicus

<400> 10

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Met Ala Ser Pro Arg Leu Gly Ile Phe Cys Cys Pro Ser Trp Asp Ala
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Ala Thr Gln Leu Val Leu Thr Phe Gln Pro Arg Val Phe His Ala Leu
            20                  25                  30

Cys Leu Gly Ser Gly Ala Leu Arg Leu Val Leu Gly Leu Leu Gln Leu
        35                  40                  45

Leu Thr Gly Arg Arg Ser Val Gly His Arg Ala Pro Ala Thr Thr Pro
    50                  55                  60

Ala Ala Ser Val His Ile Leu Arg Ala Ala Thr Ala Cys Asp Leu Leu
65                  70                  75                  80

Gly Cys Leu Gly Ile Val Ile Arg Ser Thr Val Trp Ile Ala Tyr Pro
                85                  90                  95

Glu Phe Ile Glu Asn Ile Ser Asn Met Asn Gly Thr Asp Ile Trp Pro
            100                 105                 110

Thr Ala Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Leu Tyr Ser
        115                 120                 125

Ala Cys Phe Trp Trp Leu Phe Cys Tyr Ala Val Asp Val Tyr Leu Val
    130                 135                 140

Ile Arg Arg Ser Ala Gly Arg Ser Thr Ile Leu Leu Tyr His Ile Met
145                 150                 155                 160

Ala Trp Gly Leu Pro Val Leu Leu Cys Val Glu Gly Ala Val Met Leu
```

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                 165                 170                 175

Tyr Tyr Pro Ser Val Ser Arg Cys Glu Arg Gly Leu Asp His Ala Ile
            180                 185                 190

Pro His Tyr Val Thr Thr Tyr Leu Pro Leu Met Leu Val Leu Val Ala
        195                 200                 205

Asn Pro Ile Leu Phe His Lys Thr Val Ile Ser Val Ala Ser Leu Leu
    210                 215                 220

Lys Gly Arg Lys Gly Val Tyr Thr Glu Asn Glu Arg Leu Met Gly Ala
225                 230                 235                 240

Val Ile Lys Thr Arg Phe Phe Lys Ile Met Leu Val Leu Ile Ala Cys
                245                 250                 255

Trp Leu Ser Asn Ile Ile Asn Glu Cys Leu Leu Phe Tyr Leu Glu Met
            260                 265                 270

Gln Pro Asp Thr His Gly Gly Ser Leu Lys Arg Ile Gln Asn Ala Ala
        275                 280                 285

Arg Thr Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Ser Gln Gly Leu
    290                 295                 300

Leu Leu Ser Leu Ala Phe Tyr Gly Trp Thr Gly Cys Ser Leu Asp Val
305                 310                 315                 320

His Ala Pro Lys Met Val Ile Gln Trp Glu Thr Met Thr Ala Ser Ala
                325                 330                 335

Ala Glu Gly Thr Tyr Gln Thr Pro Glu Gly Ser Cys Val Pro His Gln
            340                 345                 350

Asn Pro Arg Lys Val Val Cys Val Gly Gly His Thr Ser Asp Glu Val
        355                 360                 365

Leu Ser Ile Leu Ser Glu Gly Ser Asp Ala Ser Thr Val Glu Ile His
    370                 375                 380

Thr Ala Thr Gly Ser His Asn Ile Lys Glu Val Asp Ser Ile Ser Gln
385                 390                 395                 400

Ala Gln Gly Asp Leu
                405
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<210> 11
<211> 425
<212> DNA
<213> Ornithorhynchus anatinus

<400> 11

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ctcctgctca gcatcttcca gctccttccc aaacgaggcc aaggccccag gaaactaact 180

caaacctcct ctgccagcat cctgctcttc atctctgcct gtgaccttct tggctgtctg 240

ggtgtaatat tcaggtccac agtgtggtta ggattcccag atttcgttgg aaacatctcg 300

gtggtgaatg ggacagatgg atggccctca gctttctgtg tagggagtgc aatgtggatt 360

caactgctgt acagtgcttg cttctggtgg cttgtttgct atgctgtaga tgccttacct 420

tgctt 425

<210> 12
<211> 141
<212> PRT
<213> Ornithorhynchus anatinus

<400> 12

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Met Ala Ser Pro Arg Leu Glu Thr Phe Cys Cys Pro Asn Arg Asp Ala
1               5                  10                  15

Ala Thr Gln Leu Met Leu Asn Phe Gln Pro Gln Ile Phe Asn Gly Val
            20                  25                  30

Cys Leu Gly Ser Ala Ser Ala Asn Leu Leu Leu Ser Ile Phe Gln Leu
        35                  40                  45

Leu Pro Lys Arg Gly Gln Gly Pro Arg Lys Leu Thr Gln Thr Ser Ser
    50                  55                  60

Ala Ser Ile Leu Leu Phe Ile Ser Ala Cys Asp Leu Leu Gly Cys Leu
65                  70                  75                  80

Gly Val Ile Phe Arg Ser Thr Val Trp Leu Gly Phe Pro Asp Phe Val
                85                  90                  95

Gly Asn Ile Ser Val Val Asn Gly Thr Asp Gly Trp Pro Ser Ala Phe
            100                 105                 110

Cys Val Gly Ser Ala Met Trp Ile Gln Leu Leu Tyr Ser Ala Cys Phe
        115                 120                 125

Trp Trp Leu Val Cys Tyr Ala Val Asp Ala Leu Pro Cys
                130                 135                 140
```

<210> 13
<211> 1800
<212> DNA
<213> Xenopus laevis

<400> 13

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atatcatccc caggtttcat tagtaatatg tcactaatga atacttcaga catctggcct 540

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tggttatttt gctatgcaat tgatgcttac ctagttgttc gcagatctgc aggaataagc 660

acaattgtgt tgtatcacat gatgacgtgg ggcctggcac ttatgctctg cgttgaaggt 720

gtggctatgc tttactatcc ttcagtttcc aattgtgaaa atggactaga acatgcaatt 780

cctcattatg tcacaaccta tgcaccactt cttatcgtaa tgtttgcgaa tccaatcctc 840

tttcgaagaa cagttgcagc agttgcttct ttactgaaag gaagacaagg aatttataca 900

gagaatgaaa gacggctggg gacagaaatt caactccgtt ttttcaagat catgttggtg 960

tttatgatct gttggacagc taatattatc aatgagactc ttttgttcta cctggaaatg 1020

cagccagaca tcaaaacgga tcagctaaag aatgtcagga atgcagcact catcacatgg 1080

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caataatggg tacctggcaa tatgaagaag caattgcaat gactgaattt aaaacacatt 1560

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<210> 14

<211> 400
<212> PRT
<213> Xenopus laevis

<400> 14

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Met Ala Ser Pro Arg Leu Glu Thr Phe Cys Cys Pro Asn Arg Asp Ala
1               5                  10                  15

Ala Thr Gln Leu Val Leu Asp Phe Gln Pro Gln Val Tyr Gly Ser Leu
            20                  25                  30

Cys Leu Gly Ser Gly Leu Val Ser Leu Leu Leu Thr Ile Val Gln Leu
        35                  40                  45

Leu Pro Lys Thr Lys His Gly Tyr Arg Arg His Gly Arg Ser Met Leu
    50                  55                  60

Pro Lys Pro Ser Ser Ser Arg Ile Leu Phe Leu Val Ile Val Cys Asp
65                  70                  75                  80

Leu Leu Gly Cys Leu Gly Ile Leu Ile Arg Ser Ser Val Trp Ile Ser
                85                  90                  95

Ser Pro Gly Phe Ile Ser Asn Met Ser Leu Met Asn Thr Ser Asp Ile
            100                 105                 110

Trp Pro Ser Ser Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Phe
        115                 120                 125

Tyr Ser Ala Ser Phe Trp Trp Leu Phe Cys Tyr Ala Ile Asp Ala Tyr
    130                 135                 140

Leu Val Val Arg Arg Ser Ala Gly Ile Ser Thr Ile Val Leu Tyr His
145                 150                 155                 160

Met Met Thr Trp Gly Leu Ala Leu Met Leu Cys Val Glu Gly Val Ala
                165                 170                 175

Met Leu Tyr Tyr Pro Ser Val Ser Asn Cys Glu Asn Gly Leu Glu His
            180                 185                 190

Ala Ile Pro His Tyr Val Thr Thr Tyr Ala Pro Leu Leu Ile Val Met
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195 200 205

Phe Ala Asn Pro Ile Leu Phe Arg Arg Thr Val Ala Ala Val Ala Ser
210 215 220

Leu Leu Lys Gly Arg Gln Gly Ile Tyr Thr Glu Asn Glu Arg Arg Leu
225 230 235 240

Gly Thr Glu Ile Gln Leu Arg Phe Phe Lys Ile Met Leu Val Phe Met
245 250 255

Ile Cys Trp Thr Ala Asn Ile Ile Asn Glu Thr Leu Leu Phe Tyr Leu
260 265 270

Glu Met Gln Pro Asp Ile Lys Thr Asp Gln Leu Lys Asn Val Arg Asn
275 280 285

Ala Ala Leu Ile Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Met Gln
290 295 300

Gly Phe Leu Phe Thr Leu Ala Phe Tyr Gly Trp Thr Gly Trp Asn Val
305 310 315 320

Asp Phe Asn Phe Arg Gln Lys Glu Thr Ala Trp Glu Arg Val Ser Thr
325 330 335

Ser Ser Leu Thr Glu Ala Ala His Asn Gly Thr Asn Gly Ser Phe Leu
340 345 350

Asp Tyr Pro Gly Tyr Ile Gln Asn Gln Asn Lys Thr Glu Ile Gly Asn
355 360 365

Ser Gln Gln Thr Asp Glu Ala Leu Ser Ile Leu Ser Glu Gly Asn Gly
370 375 380

Ser Ile Val Glu Arg Leu Ser Arg Asn Ser Pro Val Tyr Gln Gly Trp
385 390 395 400

<210> 15
<211> 1622
<212> DNA
<213> Gallus gallus

<400> 15

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ccgtcccttt ccagctgtga aagaggcctg gagcatgcaa tcccacatta catcacaacc 660

tatgccccac tcctgctggt gctggtggtc aacccagtcc tgttcagaag gacggtgact 720

gcagttgcct ctttactgaa agggagacaa gggatttaca cagagaatga gagacggctg 780

gggacagaga tccagatgcg ctttttcaag attatgctgg tattcactgt ttgctggtca 840

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acacctttga aaaacattag aagtgctgca ttgatcacat ggattataat gggagttctt 960

aatccgatgc aaggcttcct cttcacatta gctttctatg gctggacagg atggaaagtg 1020

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gacaatgact atccctcacc agtgaactac caaagcaacg tccacgattc aaagaagata 1140

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tt 1622

<210> 16
<211> 392
<212> PRT
<213> Gallus gallus

<400> 16

Met Ala Ser Pro Arg Leu Glu Thr Tyr Cys Cys Pro Asn Arg Asp Ala
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Ala Thr Gln Leu Val Met Asn Phe Gln Pro Gln Val Phe Cys Gly Val

```
            20                  25                  30

Cys Ile Gly Ser Ala Ser Ala Ser Leu Leu Leu Thr Ile Leu Gln Leu
        35                  40                  45

Leu Pro Lys Lys Gly Gln Ser Leu Arg Lys Met Pro Lys Ala Ser Ser
    50                  55                  60

Ser Ser Thr Ile Leu Leu Leu Ile Ser Val Cys Asp Ile Leu Gly Gly
65                  70                  75                  80

Ser Gly Val Ile Phe Arg Ser Ser Val Trp Leu Gly Phe Pro Ser Phe
                85                  90                  95

Ile Ala Asn Ile Ser Val Ala Asn Gly Thr Asp Ile Trp Pro Ser Ala
            100                 105                 110

Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Leu Tyr Ser Ala Gly
        115                 120                 125

Phe Trp Trp Leu Phe Cys Tyr Ala Val Asp Ser Tyr Leu Val Val Arg
    130                 135                 140

Arg Ser Ala Gly Arg Ser Thr Ile Val Leu Tyr His Met Met Ala Trp
145                 150                 155                 160

Gly Leu Ala Val Leu Leu Cys Met Glu Gly Val Met Leu Leu Tyr Tyr
                165                 170                 175

Pro Ser Leu Ser Ser Cys Glu Arg Gly Leu Glu His Ala Ile Pro His
            180                 185                 190

Tyr Ile Thr Thr Tyr Ala Pro Leu Leu Leu Val Leu Val Val Asn Pro
        195                 200                 205

Val Leu Phe Arg Arg Thr Val Thr Ala Val Ala Ser Leu Leu Lys Gly
    210                 215                 220

Arg Gln Gly Ile Tyr Thr Glu Asn Glu Arg Arg Leu Gly Thr Glu Ile
225                 230                 235                 240

Gln Met Arg Phe Phe Lys Ile Met Leu Val Phe Thr Val Cys Trp Ser
                245                 250                 255

Ser Asn Ile Ile Asn Glu Ser Leu Leu Phe Tyr Leu Glu Met Gln Pro
            260                 265                 270
```

```
Asp Ile Asn Glu Thr Pro Leu Lys Asn Ile Arg Ser Ala Ala Leu Ile
        275                 280                 285

Thr Trp Ile Ile Met Gly Val Leu Asn Pro Met Gln Gly Phe Leu Phe
    290                 295                 300

Thr Leu Ala Phe Tyr Gly Trp Thr Gly Trp Lys Val Asp Leu Lys Trp
305                 310                 315                 320

Gln Lys Arg Glu Ile Pro Trp Glu Ser Met Ser Ser Ser Thr Val Gly
                325                 330                 335

Asp Asn Asp Tyr Pro Ser Pro Val Asn Tyr Gln Ser Asn Val His Asp
            340                 345                 350

Ser Lys Lys Ile Ser Thr Thr Asp Ser Gln Gln Thr Asp Glu Ala Ile
        355                 360                 365

Ser Met Leu Ser Glu Gly Asn Thr Ser Ser Asp Asp Arg Leu Thr Arg
    370                 375                 380

Ser Ser Ala Ile Tyr Gln Gly Trp
385                 390
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<210> 17
<211> 1712
<212> DNA
<213> Danio rerio

<400> 17

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tggacgggtc tggatctgga cttcagtcgg cagagacgtc gcgagctgcc ctgggactcg 1140

gcctccacat ctcttgctgg aggattcact cctgtggtcg gatcatcttt aatttaccag 1200

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cttttgagtg ttttgtttta atcctctgta attcagtgta cactattacg tgcttcgggt 1620

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<210> 18
<211> 412
<212> PRT

<213> Danio rerio

<400> 18

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Met Ala Ser Pro Arg Leu Glu Thr Phe Cys Cys Pro Asn Arg Asp Gly
1               5                  10                  15

Ala Thr Glu Leu Val Val Gly Phe Gln Pro Leu Phe Phe Gly Val Met
            20                  25                  30

Cys Val Cys Ser Ala Ala Leu Ser Ser Gly Leu Ala Leu Leu Gln Ile
        35                  40                  45

Leu Pro Lys Arg Arg Ser Phe Arg Pro Gln Ala His Ser Ser Arg Ala
    50                  55                  60

Ala Ser Ser Ser Arg Ile Leu Thr Ile Ile Ser Val Cys Asp Ile Leu
65                  70                  75                  80

Gly Cys Thr Gly Ile Ile Ile Arg Ser Ser Leu Trp Ile Gly Leu Pro
                85                  90                  95
```

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Asn Leu Val Ser Glu Ile Ser Asp Gly Asn Ser Ser Ser Val Trp Pro
            100                 105                 110

Gln Val Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Phe Phe Ser
        115                 120                 125

Ala Ser Phe Trp Trp Thr Phe Cys Tyr Ala Val Asp Val Phe Leu Val
    130                 135                 140

Val Lys Arg Ser Ala Gly Ile Ser Thr Ile Ile Leu Tyr His Met Ile
145                 150                 155                 160

Thr Trp Gly Leu Thr Leu Leu Leu Cys Val Glu Gly Val Ala Met Leu
                165                 170                 175

Tyr Tyr Pro Ser Ile Ser Ser Cys Glu Asn Gly Leu Gln His Ala Ile
            180                 185                 190

Pro His Tyr Val Thr Thr Tyr Ala Pro Met Leu Leu Val Leu Ala Val
        195                 200                 205

Asn Pro Val Leu Phe Thr Arg Thr Val Ser Ala Val Thr Ser Leu Leu
    210                 215                 220

Lys Gly Gln Gln Gly Ile Tyr Thr Glu Asn Glu Arg Arg Leu Gly Ser
225                 230                 235                 240

Glu Ile Lys Ile Arg Phe Phe Lys Ile Met Leu Val Phe Phe Ile Cys
                245                 250                 255

Trp Leu Pro Asn Ile Ile Asn Glu Ser Leu Leu Phe Tyr Leu Glu Met
            260                 265                 270

Gln Asp Asp Val Lys Ser Ser Asp Leu Lys Asn Ile Arg Asn Ala Ala
        275                 280                 285

Leu Ile Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Met Gln Gly Phe
    290                 295                 300

Leu Asn Thr Leu Ala Phe His Gly Trp Thr Gly Leu Asp Leu Asp Phe
305                 310                 315                 320

Ser Arg Gln Arg Arg Arg Glu Leu Pro Trp Asp Ser Ala Ser Thr Ser
                325                 330                 335

Leu Ala Gly Gly Phe Thr Pro Val Val Gly Ser Ser Leu Ile Tyr Gln
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340 345 350

Ser His Val Gln Glu Ile Lys Lys Asn Leu Ser Ala Asn Gly Gly Gln
355 360 365

Gln Pro Ser Asp Ala Ile Ser Val Leu Ser Glu Asp Ser Glu Ser Ser
370 375 380

Thr Val Glu Ile His Ile Ser Ser Glu Gln Arg Glu Phe Glu Glu Leu
385 390 395 400

Lys Arg Asn Gly Ala Ser Trp Glu Ile Ser Thr Gly
405 410

<210> 19
<211> 1476
<212> DNA
<213> Pan troglodytes

<400> 19

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<210> 20

<400> 20
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<210> 21
<211> 1770
<212> DNA
<213> Macaca mulatta

<400> 21

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catcccccac tatgtcacca tgtacctgcc cctgctgctg gttctcatgg ccaaccccat 780

cctgttccaa aagacagtga ctgcagtggc ctctttactt aaaggaagac aaggcattta 840

cacggagaac gagagaagga tgggagctgt gatcaagatc cgatttttca agataatgct 900

ggttttaatt atttgttggt tgtcgaatat catcaatgaa agccttttat tctatcttga 960

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atggtttatt atgggaatcc tgaatccagc ccagggattt ctcttgtctt tggccttcta 1080

tggctggaca ggatgtagcc tgggttttca gtctcccagg aaggagatcc agtgggaatc 1140

actgaccacc tcggctgctg atggggctca cccatccccg ctggactccc gggtgcccca 1200

ggaaaaccct gcttccaaga aggtgtctcg agtgggtggg cagacttctg atgaagccct 1260

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<210> 22
<211> 407
<212> PRT
<213> Macaca mulatta

<400> 22

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Met Ala Ser Pro Arg Leu Gly Thr Phe Cys Cys Pro Thr Arg Asp Ala
1               5                  10                  15

Ala Thr Gln Leu Val Leu Ser Phe Gln Pro Arg Ala Phe His Ala Leu
            20                  25                  30

Cys Leu Gly Ser Gly Ala Leu Arg Leu Ala Leu Gly Leu Leu Gln Leu
        35                  40                  45

Leu Pro Gly Arg Arg Pro Ala Gly Pro Gly Ser Pro Ala Thr Ser Pro
    50                  55                  60

Pro Ala Ser Val Arg Ile Leu Arg Ala Ala Thr Ala Cys Asp Leu Leu
65                  70                  75                  80

Gly Cys Leu Gly Val Val Ile Arg Ser Thr Val Trp Leu Gly Phe Pro
                85                  90                  95

Asn Phe Val Asp Ser Ile Ser Asp Val Asn Arg Thr Glu Ile Trp Pro
            100                 105                 110

Ala Val Phe Cys Val Gly Ser Ala Met Trp Ile Gln Leu Leu Tyr Ser
        115                 120                 125

Ala Cys Phe Trp Trp Leu Phe Cys Tyr Ala Val Asp Ala Tyr Leu Val
    130                 135                 140
```

```
Ile Arg Arg Ser Ala Gly Leu Ser Thr Ile Leu Leu Tyr His Ile Met
145                 150                 155                 160

Ala Trp Gly Leu Ala Thr Leu Leu Cys Val Glu Gly Ala Ala Met Leu
                165                 170                 175

Tyr Tyr Pro Ser Val Ser Arg Cys Glu Arg Gly Leu Asp His Ala Ile
            180                 185                 190

Pro His Tyr Val Thr Met Tyr Leu Pro Leu Leu Leu Val Leu Met Ala
        195                 200                 205

Asn Pro Ile Leu Phe Gln Lys Thr Val Thr Ala Val Ala Ser Leu Leu
    210                 215                 220

Lys Gly Arg Gln Gly Ile Tyr Thr Glu Asn Glu Arg Arg Met Gly Ala
225                 230                 235                 240

Val Ile Lys Ile Arg Phe Phe Lys Ile Met Leu Val Leu Ile Ile Cys
                245                 250                 255

Trp Leu Ser Asn Ile Ile Asn Glu Ser Leu Leu Phe Tyr Leu Glu Met
            260                 265                 270

Gln Thr Asp Ile Asn Gly Gly Ser Leu Lys Pro Val Arg Thr Ala Ala
        275                 280                 285

Lys Thr Thr Trp Phe Ile Met Gly Ile Leu Asn Pro Ala Gln Gly Phe
    290                 295                 300

Leu Leu Ser Leu Ala Phe Tyr Gly Trp Thr Gly Cys Ser Leu Gly Phe
305                 310                 315                 320

Gln Ser Pro Arg Lys Glu Ile Gln Trp Glu Ser Leu Thr Thr Ser Ala
                325                 330                 335

Ala Asp Gly Ala His Pro Ser Pro Leu Asp Ser Arg Val Pro Gln Glu
            340                 345                 350

Asn Pro Ala Ser Lys Lys Val Ser Arg Val Gly Gly Gln Thr Ser Asp
        355                 360                 365

Glu Ala Leu Ser Met Leu Ser Glu Gly Ser Asp Ala Ser Thr Ile Glu
    370                 375                 380

Ile His Thr Ala Ser Glu Ser Cys Asn Lys Asn Glu Ala Asp Pro Ala
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385 390 395 400

Leu Pro Thr His Gly Asp Leu
405

<210> 23
<211> 517
<212> DNA
<213> Rhesus macaque

<400> 23

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gcttcttccc gaagagcctt taggataggt gaaatgattc atgcatatgc gtgtgggaat 360

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<210> 24

<400> 24
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<210> 25
<211> 1542
<212> DNA
<213> Homo sapiens

<400> 25

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ctgggtgtgg agctgcagcg tatccacagg ccccaggatg caggccctgg tgctactcct 180

ctgcattgga gccctcctcg ggcacagcag ctgccagaac cctgccagcc ccccggagga 240

gggctcccca gaccccgaca gcacaggggc gctggtggag gaggaggatc ctttcttcaa 300

agtccccgtg aacaagctgg cagcggctgt ctccaacttc ggctatgacc tgtaccgggt 360

gcgatccagc acgagcccca cgaccaacgt gctcctgtct cctctcagtg tggccacggc 420

cctctcggcc ctctcgctgg gagcggagca gcgaacagaa tccatcattc accgggctct 480

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ggtcactgcc ccccagaaga acctcaagag tgcctcccgg atcgtctttg agaagaagct 600

gcgcataaaa tccagctttg tggcacctct ggaaaagtca tatgggacca ggcccagagt 660

cctgacgggc aaccctcgct tggacctgca agagatcaac aactgggtgc aggcgcagat 720

gaaagggaag ctcgccaggt ccacaaagga aattcccgat gagatcagca ttctccttct 780

cggtgtggcg cacttcaagg ggcagtgggt aacaaagttt gactccagaa agacttccct 840

cgaggatttc tacttggatg aagagaggac cgtgagggtc cccatgatgt cggaccctaa 900

ggctgtttta cgctatggct tggattcaga tctcagctgc aagattgccc agctgccctt 960

gaccggaagc atgagtatca tcttcttcct gcccctgaaa gtgacccaga atttgacctt 1020

gatagaggag agcctcacct ccgagttcat tcatgacata gaccgagaac tgaagaccgt 1080

gcaggcggtc ctcactgtcc ccaagctgaa gctgagttat gaaggcgaag tcaccaagtc 1140

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cattggcaag attctggacc ccaggggccc ctaatatccc agtttaatat tccaataccc 1440

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tcaatgcata caataaaaga gctttatccc taacttctgt ta 1542

<210> 26
<211> 418
<212> PRT
<213> Homo sapiens

<400> 26

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Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
1               5                  10                  15

Ser Ser Cys Gln Asn Pro Ala Ser Pro Pro Glu Glu Gly Ser Pro Asp
            20                  25                  30

Pro Asp Ser Thr Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys
        35                  40                  45

Val Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp
    50                  55                  60

Leu Tyr Arg Val Arg Ser Ser Thr Ser Pro Thr Thr Asn Val Leu Leu
65                  70                  75                  80

Ser Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala
                85                  90                  95
```

```
Glu Gln Arg Thr Glu Ser Ile Ile His Arg Ala Leu Tyr Tyr Asp Leu
            100                 105                 110

Ile Ser Ser Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Asp Thr
        115                 120                 125

Val Thr Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe
    130                 135                 140

Glu Lys Lys Leu Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys
145                 150                 155                 160

Ser Tyr Gly Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp
                165                 170                 175

Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu
            180                 185                 190

Ala Arg Ser Thr Lys Glu Ile Pro Asp Glu Ile Ser Ile Leu Leu Leu
        195                 200                 205

Gly Val Ala His Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg
    210                 215                 220

Lys Thr Ser Leu Glu Asp Phe Tyr Leu Asp Glu Glu Arg Thr Val Arg
225                 230                 235                 240

Val Pro Met Met Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp
                245                 250                 255

Ser Asp Leu Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
            260                 265                 270

Ser Ile Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu
        275                 280                 285

Ile Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu
    290                 295                 300

Leu Lys Thr Val Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser
305                 310                 315                 320

Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Met Lys Leu Gln Ser
                325                 330                 335

Leu Phe Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys
            340                 345                 350
```

Leu Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly
355 360 365

Ala Gly Thr Thr Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe
370 375 380

Pro Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp
385 390 395 400

Thr Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg
405 410 415

Gly Pro

<210> 27
<211> 2105
<212> DNA
<213> Rattus norvegicus

<400> 27

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gagcggtcgc cgaaatgttc cggtgtggag gcctggcggg tgctttcaag cagaaactgg 120

tgcccttggt gcggtcggtg tgcgtccaga ggccgaaaca gaggaaccgg cttccaggca 180

acttgttcca gcaatggcgt gttcctctag aactccagat ggcaagacaa atggctagct 240

ctggtccatc agggggcaaa atggataatt ctgtgttagt ccttattgtg ggcttatcaa 300

caataggagc tggtgcatat gcctacaaga ctattaaaga agaccaaaaa agatataatg 360

aaagaataat gggattagga ctgtcaccag aagagaaaca gagaagagcc attgcctctg 420

ctgcagaagg aggctcagtt cctccaatca gggtaccaag tcacgtccct ttcctgctga 480

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aagaattgtg gttttcagat gacccaaatg tcacaaagac actgcagttc agacagtgga 660

atggaaaaga gagaagcatc tatttccagc caccttcttt ctatgtctct gctcaggacc 720

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acgctgttgt gagtggaaga ctggctggag aaaatatgac tggagctgct aagccatact 1500

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tggtggatag tagtttgccc acagttggtg tttttgcaaa agcaactgca caagacaacc 1620

caaaatctgc cacagagcag tcaggaactg gtatccgttc ggagagtgag acagagtctg 1680

aagcttctga aatcacaatc cctcccagtg accctgcagt cccacaggtc cctgttgaag 1740

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ttttattcag catacttttt ctttatgtag gagcaggaat cgaacaagcc tctgtgaata 2040

ttttcatctg tataaatgca catcacaaat taaaatctga ttcttttcaa aaaaaaagcg 2100

gccgc 2105

<210> 28
<211> 612
<212> PRT
<213> Rattus norvegicus

<400> 28

Met Phe Arg Cys Gly Gly Leu Ala Gly Ala Phe Lys Gln Lys Leu Val
1 5 10 15

Pro Leu Val Arg Ser Val Cys Val Gln Arg Pro Lys Gln Arg Asn Arg
20 25 30

Leu Pro Gly Asn Leu Phe Gln Gln Trp Arg Val Pro Leu Glu Leu Gln
35 40 45

Met Ala Arg Gln Met Ala Ser Ser Gly Pro Ser Gly Gly Lys Met Asp
50 55 60

Asn Ser Val Leu Val Leu Ile Val Gly Leu Ser Thr Ile Gly Ala Gly
65 70 75 80

```
Ala Tyr Ala Tyr Lys Thr Ile Lys Glu Asp Gln Lys Arg Tyr Asn Glu
                85                  90                  95

Arg Ile Met Gly Leu Gly Leu Ser Pro Glu Glu Lys Gln Arg Arg Ala
            100                 105                 110

Ile Ala Ser Ala Ala Glu Gly Gly Ser Val Pro Pro Ile Arg Val Pro
        115                 120                 125

Ser His Val Pro Phe Leu Leu Ile Gly Gly Gly Thr Ala Ala Phe Ala
    130                 135                 140

Ala Ala Arg Ser Ile Arg Ala Arg Asp Pro Gly Ala Arg Val Leu Ile
145                 150                 155                 160

Val Ser Glu Asp Pro Glu Leu Pro Tyr Met Arg Pro Pro Leu Ser Lys
                165                 170                 175

Glu Leu Trp Phe Ser Asp Asp Pro Asn Val Thr Lys Thr Leu Gln Phe
            180                 185                 190

Arg Gln Trp Asn Gly Lys Glu Arg Ser Ile Tyr Phe Gln Pro Pro Ser
        195                 200                 205

Phe Tyr Val Ser Ala Gln Asp Leu Pro His Ile Glu Asn Gly Gly Val
    210                 215                 220

Ala Val Leu Thr Gly Lys Lys Val Val His Leu Asp Val Arg Gly Asn
225                 230                 235                 240

Met Val Lys Leu Asn Asp Gly Ser Gln Ile Thr Phe Glu Lys Cys Leu
                245                 250                 255

Ile Ala Thr Gly Gly Thr Pro Arg Ser Leu Ser Ala Ile Asp Arg Ala
            260                 265                 270

Gly Ala Glu Val Lys Ser Arg Thr Thr Leu Phe Arg Lys Ile Gly Asp
        275                 280                 285

Phe Arg Ala Leu Glu Lys Ile Ser Arg Glu Val Lys Ser Ile Thr Val
    290                 295                 300

Ile Gly Gly Gly Phe Leu Gly Ser Glu Leu Ala Cys Ala Leu Gly Arg
305                 310                 315                 320

Lys Ser Gln Ala Ser Gly Ile Glu Val Ile Gln Leu Phe Pro Glu Lys
```

325 330 335

Gly Asn Met Gly Lys Ile Leu Pro Glu Tyr Leu Ser Asn Trp Thr Met
340 345 350

Glu Lys Val Lys Arg Glu Gly Val Lys Val Met Pro Asn Ala Ile Val
355 360 365

Gln Ser Val Gly Val Ser Gly Gly Lys Leu Leu Ile Lys Leu Lys Asp
370 375 380

Gly Arg Lys Val Glu Thr Asp His Ile Val Thr Ala Val Gly Leu Glu
385 390 395 400

Pro Asn Val Glu Leu Ala Lys Thr Gly Gly Leu Glu Ile Asp Ser Asp
405 410 415

Phe Gly Gly Phe Arg Val Asn Ala Glu Leu Gln Ala Arg Ser Asn Ile
420 425 430

Trp Val Ala Gly Asp Ala Ala Cys Phe Tyr Asp Ile Lys Leu Gly Arg
435 440 445

Arg Arg Val Glu His His Asp His Ala Val Val Ser Gly Arg Leu Ala
450 455 460

Gly Glu Asn Met Thr Gly Ala Ala Lys Pro Tyr Trp His Gln Ser Met
465 470 475 480

Phe Trp Ser Asp Leu Gly Pro Asp Val Gly Tyr Glu Ala Ile Gly Leu
485 490 495

Val Asp Ser Ser Leu Pro Thr Val Gly Val Phe Ala Lys Ala Thr Ala
500 505 510

Gln Asp Asn Pro Lys Ser Ala Thr Glu Gln Ser Gly Thr Gly Ile Arg
515 520 525

Ser Glu Ser Glu Thr Glu Ser Glu Ala Ser Glu Ile Thr Ile Pro Pro
530 535 540

Ser Asp Pro Ala Val Pro Gln Val Pro Val Glu Gly Glu Asp Tyr Gly
545 550 555 560

Lys Gly Val Ile Phe Tyr Leu Arg Asp Lys Val Val Val Gly Ile Val
565 570 575

```
Leu Trp Asn Val Phe Asn Arg Met Pro Ile Ala Arg Lys Ile Ile Lys
            580                 585                 590

Asp Gly Glu Gln His Glu Asp Leu Asn Glu Val Ala Lys Leu Phe Asn
        595                 600                 605

Ile His Glu Asp
    610
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<210> 29
<211> 1486
<212> DNA
<213> Taeniopygia guttata

<400> 29

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cttaactgtc ccaagcagaa cccagaactc agctaccgag cagaactctg ccacagctga 180

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agagcatgaa aagtgcctcc cggatcatct tggagaaaag actcagggca aggcctggat 540

ttcacagcca gctcgagaag tcctacaaga tgcgaccaag agcactgagt ggcaacaccc 600

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ggttcatgaa ggacatgccc acagatgtca gcattctcct tgctggggct gctttcttca 720

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cttctgagtt tgtccacgat gtggacaagg agctgaagac agtccacgct gtgctgagct 1020

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ggtgatattg ggagggatac tggctccctg ctctgctgca caaagacaca acttgcaaat 1440

cttacgcctt catgctgcaa taaaagagct tttgctatta atctca 1486

<210> 30
<211> 385
<212> PRT
<213> Taeniopygia guttata

<400> 30

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Met Glu Pro Met Leu Gly Glu Glu Glu Glu Asp Pro Phe Tyr Lys Ser
1               5                  10                  15

Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu
            20                  25                  30

Tyr Arg Gln Gln Ser Ile Arg Thr Ala Thr Ala Asn Val Leu Leu Ser
        35                  40                  45

Pro Phe Ser Leu Ala Thr Ala Leu Ser Gly Leu Ser Leu Gly Ala Gly
    50                  55                  60

Glu Arg Thr Glu Asp Val Ile Ser Arg Ala Leu Phe Tyr Asp Leu Leu
65                  70                  75                  80

Asn Lys Ala Glu Val His Asp Thr Tyr Lys Glu Leu Leu Ser Ser Val
                85                  90                  95

Thr Gly Pro Glu Lys Ser Met Lys Ser Ala Ser Arg Ile Ile Leu Glu
            100                 105                 110

Lys Arg Leu Arg Ala Arg Pro Gly Phe His Ser Gln Leu Glu Lys Ser
        115                 120                 125

Tyr Lys Met Arg Pro Arg Ala Leu Ser Gly Asn Thr Gln Leu Asp Leu
    130                 135                 140

Gln Glu Ile Asn Thr Trp Val Arg Gln Gln Thr Lys Gly Arg Ile Met
145                 150                 155                 160

Arg Phe Met Lys Asp Met Pro Thr Asp Val Ser Ile Leu Leu Ala Gly
                165                 170                 175

Ala Ala Phe Phe Lys Gly Thr Trp Lys Thr Lys Phe Asp Thr Lys Arg
            180                 185                 190

Thr Ala Leu Gln Asp Phe His Leu Asp Glu Asp Arg Thr Val Lys Val
        195                 200                 205
```

Ser Met Met Ser Asp Pro Lys Ala Ile Leu Arg Tyr Gly Phe Asp Ser
210 215 220

Glu Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Glu Gly Ile Ser
225 230 235 240

Ala Met Phe Phe Leu Pro Thr Lys Val Thr Gln Asn Met Thr Leu Ile
245 250 255

Glu Glu Ser Leu Thr Ser Glu Phe Val His Asp Val Asp Lys Glu Leu
260 265 270

Lys Thr Val His Ala Val Leu Ser Leu Pro Lys Leu Lys Leu Asn His
275 280 285

Glu Glu Ala Leu Gly Ser Thr Leu Lys Glu Thr Arg Leu Gln Ser Leu
290 295 300

Phe Thr Ser Pro Asp Phe Ser Lys Ile Ser Ala Lys Pro Leu Arg Leu
305 310 315 320

Ser His Val Gln His Lys Ala Met Leu Glu Leu Gly Glu Asp Gly Glu
325 330 335

Arg Ser Thr Pro Asn Ala Gly Ala Asn Ala Ala Arg Leu Thr Phe Pro
340 345 350

Ile Glu Tyr His Val Asp Arg Pro Phe Leu Leu Val Leu Arg Asp Asp
355 360 365

Thr Thr Gly Thr Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly
370 375 380

Val
385

<210> 31
<211> 1464
<212> DNA
<213> Equus caballus

<400> 31

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tcgctggggg cggaacagcg gacagagtcc agcattcacc tggctctcta ctatgacctg 420

atcaagaacc cagacatcca cggcacctac aaggaactcc ttgcgtccgt cactgccccc 480

aataagaact tcaagagcgc ttcccgaatc atcttcgaga agaagctgcg catcaaatcc 540

agctttgtta caccactgga gaagtcatat gggaccaggc ccaagatcct gactggcaac 600

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gctaggtcca caagggaagt gcccagtgaa atcagcattc tccttctcgg tgtggcttac 720

ttcaaggggc agtgggtaac aaagtttgac tccagaaaga cttccctcca ggatttccac 780

ttggatgagg agaggaccgt gacagtcccc acgatgtcag atccgaaggc cattctacgc 840

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agcatcgtct tcttcctgcc tcagaaagtg acccagaacc tgaccatgat agaagagagc 960

ctcacctccg agttccttca tgacatagac cgagagctga agactgtgca ggcagtcctg 1020

accatcccca agctgaagct gagttatgag ggtgaagtca ctaagtccct gcaggagata 1080

aagctgcaat ccttgtttga ttcaccagac tttagcaaga tcacaggcaa acctctcaag 1140

cttactcaag tggaacatcg tgctggcttt gagtggaatg aggatggggc aaccaacccc 1200

agccaagggc cccagcctgc ccacctcacc ttccccttgg actaccacct taaccaacct 1260

ttcatctttg tactgaggga cacggacaca ggggcccttc tcttcatagg caaaattctg 1320

gaccccaggg gcacttaatg ctctagctta atgttcaaat accctagatg aagaaaaccc 1380

tagagggatg gcagattata tattacgtga aggctgccct ataatgtttc aatgtatcct 1440

tttcaataaa agtgctttat cctt 1464

<210> 32
<211> 417
<212> PRT
<213> Equus caballus

<400> 32

Met Gln Ala Leu Met Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly His
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Gly Ser Cys Gln Asn Asn Ala Gly Gly Pro Glu Glu Gly Ser Pro Asp
20 25 30

Pro Asp Ile Thr Gly Ala Pro Val Glu Glu Glu Asp Pro Phe Leu Lys
35 40 45

```
Val Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp
    50                  55                  60

Leu Tyr Arg Ala Lys Ser Ser Met Ser Pro Thr Ala Asn Val Leu Leu
65                  70                  75                  80

Ser Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala
                85                  90                  95

Glu Gln Arg Thr Glu Ser Ser Ile His Leu Ala Leu Tyr Tyr Asp Leu
            100                 105                 110

Ile Lys Asn Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Ala Ser
        115                 120                 125

Val Thr Ala Pro Asn Lys Asn Phe Lys Ser Ala Ser Arg Ile Ile Phe
    130                 135                 140

Glu Lys Lys Leu Arg Ile Lys Ser Ser Phe Val Thr Pro Leu Glu Lys
145                 150                 155                 160

Ser Tyr Gly Thr Arg Pro Lys Ile Leu Thr Gly Asn Ser Arg Thr Asp
                165                 170                 175

Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Ile
            180                 185                 190

Ala Arg Ser Thr Arg Glu Val Pro Ser Glu Ile Ser Ile Leu Leu Leu
        195                 200                 205

Gly Val Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg
    210                 215                 220

Lys Thr Ser Leu Gln Asp Phe His Leu Asp Glu Glu Arg Thr Val Thr
225                 230                 235                 240

Val Pro Thr Met Ser Asp Pro Lys Ala Ile Leu Arg Tyr Gly Leu Asp
                245                 250                 255

Ser Asp Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
            260                 265                 270

Ser Ile Val Phe Phe Leu Pro Gln Lys Val Thr Gln Asn Leu Thr Met
        275                 280                 285

Ile Glu Glu Ser Leu Thr Ser Glu Phe Leu His Asp Ile Asp Arg Glu
    290                 295                 300
```

Leu Lys Thr Val Gln Ala Val Leu Thr Ile Pro Lys Leu Lys Leu Ser
305 310 315 320

Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Ile Lys Leu Gln Ser
325 330 335

Leu Phe Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Leu Lys
340 345 350

Leu Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly
355 360 365

Ala Thr Asn Pro Ser Gln Gly Pro Gln Pro Ala His Leu Thr Phe Pro
370 375 380

Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr
385 390 395 400

Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly
405 410 415

Thr

<210> 33
<211> 1503
<212> DNA
<213> Xenopus (Silurana) tropicalis

<400> 33

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ccaagaactg acaatgaaga tctacctggc tttgcttttt acaggaagtt tcctttccta 120

caccagcgcc cagaatgctg cagatgaggt ccctacagag gtagaagaag aagatccctt 180

ctacaagagt ccaatcaaca ggcttgcctc ttctgcatct aactttggat atgacctata 240

tcgtatgcaa gcaaacaaaa atcccaacag caatatcatt atttcaccac tgagcattgc 300

tacatctctg tcaagtcttt ccttgggggg tggacaaaga actgaatcat taatccagcg 360

ttctctatac tatgaccttc tcaatgatcc tgaagtccat gctacatata aagacttgct 420

tgcaagtttt acttctcaag cgagtggatt gaaaagcaca tggcgaatca tgctggagag 480

aaggctcagg ctacggatgg attttgtgac tcaggtagag aagttctatg gaaacaagcc 540

aaaggttttg acaggaagca ctcgcctgga cctgcaggaa gccaacgact ttatacagaa 600

gcagacacaa gggaaagtgg tgaagttctt caaagagatt ccaactagtg tgagcattct 660

gctgctcgga actacttact taaaaggcca gtgggcgtac aaatttaatc ctcgggaaac 720

tgtccagcgt gaattccacc tcgatgaaca gacatctgtc actgttccaa tgatgtcatc 780

taaaaacatc cccgtgagat acggcttaga ctctgatttt aactgcaaga ttgttcagct 840

tcctctcact ggtggggtta gcatcatgtt tttcctgcca aacacagtca cccagaactt 900

gactatgatt gaagagggcc tgacatctga gtttgtccat gacatagacc aggcactgca 960

gcctatcaac ttggtcctaa gcgtccctaa actaaagctg aactatgaag ctgagcttaa 1020

ggaagcactg caggaatcaa agctccaatc ccttttcgcc actcctgact tcagcaaaat 1080

ctcctcaaag ccattaaagc tctcctatgt cgtacataaa gccaccttgg aattgaacga 1140

ggaaggagca gagacagcgc caaaaccaga ggacagccac cgcaattact ttcctttgga 1200

gtatcactta gatcatcctt tcttgtttgt tctccgtgcc aatgacaacg gcgctctcct 1260

cttcattggg aaagttatgg accctaaggg attctccttc taataaatca gtgctgtgct 1320

atctcccttt aatgttctga atgacggaga agtgcaataa attgctttgc aaaatatctc 1380

aagtcccttt ggcagagagc aactgtagct actgtactgt agccgactcc aatgccacag 1440

ttgcctgtgt tcaatcccac tgtgttatta aatcattttc cagaaaaaaa aaaaaaaaaa 1500

aaa 1503

<210> 34
<211> 409
<212> PRT
<213> Xenopus (Silurana) tropicalis

<400> 34

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Met Lys Ile Tyr Leu Ala Leu Leu Phe Thr Gly Ser Phe Leu Ser Tyr
1               5                  10                  15

Thr Ser Ala Gln Asn Ala Ala Asp Glu Val Pro Thr Glu Val Glu Glu
            20                  25                  30

Glu Asp Pro Phe Tyr Lys Ser Pro Ile Asn Arg Leu Ala Ser Ser Ala
        35                  40                  45

Ser Asn Phe Gly Tyr Asp Leu Tyr Arg Met Gln Ala Asn Lys Asn Pro
    50                  55                  60

Asn Ser Asn Ile Ile Ile Ser Pro Leu Ser Ile Ala Thr Ser Leu Ser
65                  70                  75                  80

Ser Leu Ser Leu Gly Gly Gly Gln Arg Thr Glu Ser Leu Ile Gln Arg
                85                  90                  95

Ser Leu Tyr Tyr Asp Leu Leu Asn Asp Pro Glu Val His Ala Thr Tyr
            100                 105                 110
```

```
Lys Asp Leu Leu Ala Ser Phe Thr Ser Gln Ala Ser Gly Leu Lys Ser
        115                 120                 125

Thr Trp Arg Ile Met Leu Glu Arg Arg Leu Arg Leu Arg Met Asp Phe
    130                 135                 140

Val Thr Gln Val Glu Lys Phe Tyr Gly Asn Lys Pro Lys Val Leu Thr
145                 150                 155                 160

Gly Ser Thr Arg Leu Asp Leu Gln Glu Ala Asn Asp Phe Ile Gln Lys
                165                 170                 175

Gln Thr Gln Gly Lys Val Val Lys Phe Phe Lys Glu Ile Pro Thr Ser
            180                 185                 190

Val Ser Ile Leu Leu Leu Gly Thr Thr Tyr Leu Lys Gly Gln Trp Ala
        195                 200                 205

Tyr Lys Phe Asn Pro Arg Glu Thr Val Gln Arg Glu Phe His Leu Asp
    210                 215                 220

Glu Gln Thr Ser Val Thr Val Pro Met Met Ser Ser Lys Asn Ile Pro
225                 230                 235                 240

Val Arg Tyr Gly Leu Asp Ser Asp Phe Asn Cys Lys Ile Val Gln Leu
                245                 250                 255

Pro Leu Thr Gly Gly Val Ser Ile Met Phe Phe Leu Pro Asn Thr Val
            260                 265                 270

Thr Gln Asn Leu Thr Met Ile Glu Glu Gly Leu Thr Ser Glu Phe Val
        275                 280                 285

His Asp Ile Asp Gln Ala Leu Gln Pro Ile Asn Leu Val Leu Ser Val
    290                 295                 300

Pro Lys Leu Lys Leu Asn Tyr Glu Ala Glu Leu Lys Glu Ala Leu Gln
305                 310                 315                 320

Glu Ser Lys Leu Gln Ser Leu Phe Ala Thr Pro Asp Phe Ser Lys Ile
                325                 330                 335

Ser Ser Lys Pro Leu Lys Leu Ser Tyr Val Val His Lys Ala Thr Leu
            340                 345                 350

Glu Leu Asn Glu Glu Gly Ala Glu Thr Ala Pro Lys Pro Glu Asp Ser
        355                 360                 365
```

```
His Arg Asn Tyr Phe Pro Leu Glu Tyr His Leu Asp His Pro Phe Leu
    370                 375                 380

Phe Val Leu Arg Ala Asn Asp Asn Gly Ala Leu Leu Phe Ile Gly Lys
385                 390                 395                 400

Val Met Asp Pro Lys Gly Phe Ser Phe
                405
```

<210> 35
<211> 1497
<212> DNA
<213> Mus musculus

<400> 35

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ctactcccct cactgcttcc tggagcccct cagagtgcag gctgtgagag aagctgccgc 120

aaccacagtt ccgggatgca ggccctggtg ctactcctct ggactggagc cctgctcggg 180

cacggcagca gccagaacgt ccccagcagc tctgagggct ccccagtccc ggacagcacg 240

ggcgagcccg tggaggagga ggacccctc ttcaaggtcc ctgtgaacaa gctggcagca 300

gctgtctcca acttcggcta cgatctgtac cgcctgagat ccagtgccag cccaacgggc 360

aacgtcctgc tgtctccact cagcgtggcc acggccctct ctgcctttc tctgggagct 420

gaacatcgaa cagagtctgt cattcaccgg gctctctact acgacctgat caccaaccct 480

gacatccaca gcacctacaa ggagctcctt gcctctgtta ctgcccctga gaagaacctc 540

aagagtgctt ccagaattgt gtttgagagg aaacttcgag tcaaatccag ctttgttgcc 600

cctctggaga agtcctatgg gaccaggccc cggatcctca cgggcaaccc tcgagtagac 660

cttcaggaga ttaacaactg ggtgcaggcc cagatgaaag ggaagattgc ccggtccacg 720

agggaaatgc ccagtgccct cagcatcctt ctccttggcg tggcttactt caaggggcag 780

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aggaccgtga gagtccccat gatgtcagat cctaaggcca tcttacgata cggcttggac 900

tctgatctca actgcaagat tgcccagctg cccttgacag gaagtatgag catcatcttc 960

ttcctgcccc tgaccgtgac ccagaacttg accatgatag aagagagcct cacctctgag 1020

ttcattcatg acatcgaccg agaactgaag actatccaag ctgtgctgac tgtccccaag 1080

ctgaagctga gcttcgaagg cgaacttacc aagtctctgc aggacatgaa gctacagtcg 1140

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gaacacaggg ctgctttcga gtggaatgaa gaggggcag gaagcagccc cagcccaggc 1260

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gttctgaggg acacggacac gggggccctc ctcttcatag gcagaatcct ggaccccagt 1380

agtacttaat gtctcagtgc tctacagaac ccccagaggg aagctgatta tacattccag 1440

gaaggcggcc ggtagcttca gtgtagcctc tgcaataaaa gagcttttcc ttaaaaa 1497

<210> 36
<211> 416
<212> PRT
<213> Mus musculus

<400> 36

```
Met Gln Ala Leu Val Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly His
1               5                  10                  15

Gly Ser Ser Gln Asn Val Pro Ser Ser Ser Glu Gly Ser Pro Val Pro
            20                  25                  30

Asp Ser Thr Gly Glu Pro Val Glu Glu Glu Asp Pro Phe Phe Lys Val
        35                  40                  45

Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu
    50                  55                  60

Tyr Arg Leu Arg Ser Ser Ala Ser Pro Thr Gly Asn Val Leu Leu Ser
65                  70                  75                  80

Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu
                85                  90                  95

His Arg Thr Glu Ser Val Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile
            100                 105                 110

Thr Asn Pro Asp Ile His Ser Thr Tyr Lys Glu Leu Leu Ala Ser Val
        115                 120                 125

Thr Ala Pro Glu Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe Glu
    130                 135                 140

Arg Lys Leu Arg Val Lys Ser Ser Phe Val Ala Pro Leu Glu Lys Ser
145                 150                 155                 160

Tyr Gly Thr Arg Pro Arg Ile Leu Thr Gly Asn Pro Arg Val Asp Leu
                165                 170                 175

Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Ile Ala
            180                 185                 190
```

```
Arg Ser Thr Arg Glu Met Pro Ser Ala Leu Ser Ile Leu Leu Leu Gly
        195                 200                 205

Val Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys
    210                 215                 220

Thr Thr Leu Gln Asp Phe His Leu Asp Glu Asp Arg Thr Val Arg Val
225                 230                 235                 240

Pro Met Met Ser Asp Pro Lys Ala Ile Leu Arg Tyr Gly Leu Asp Ser
                245                 250                 255

Asp Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met Ser
            260                 265                 270

Ile Ile Phe Phe Leu Pro Leu Thr Val Thr Gln Asn Leu Thr Met Ile
        275                 280                 285

Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu
    290                 295                 300

Lys Thr Ile Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser Phe
305                 310                 315                 320

Glu Gly Glu Leu Thr Lys Ser Leu Gln Asp Met Lys Leu Gln Ser Leu
                325                 330                 335

Phe Glu Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Val Lys Leu
            340                 345                 350

Thr Gln Val Glu His Arg Ala Ala Phe Glu Trp Asn Glu Glu Gly Ala
        355                 360                 365

Gly Ser Ser Pro Ser Pro Gly Leu Gln Pro Val Arg Leu Thr Phe Pro
    370                 375                 380

Leu Asp Tyr His Leu Asn Gln Pro Phe Leu Phe Val Leu Arg Asp Thr
385                 390                 395                 400

Asp Thr Gly Ala Leu Leu Phe Ile Gly Arg Ile Leu Asp Pro Ser Ser
                405                 410                 415
```

<210> 37
<211> 1810
<212> DNA
<213> Salmo salar

<400> 37

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tgtgtctggg ggccctcctc tcgctctctt atgctcagtt gttggagaca gaggcggcgg 120

gaggggaaga ggaagctgtg gagctcttta ccacgcccag agcaaagatg gccgctgcca 180

cctctgactt cggctacaac ctgttccggg ccttggcggg tcgcaacccc aatactaacg 240

tgttcctggc ccccatcagc atctctgcgg tgctcactca gctatccatg ggagcgtctc 300

cggatcgttc agagaggtgg ttatacagag ctctgaggta tcacaccctg caggaccctc 360

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ggatgactcg gttcagtcag agtggagtga tggaggactt ccagcttgtt ggagaggctc 720

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acctgggctg tacaattgct cagatccaga tgcaggatga cgtcagcatg tttgtgttcc 840

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ttcaggacct ctccatgacc cttcaccccg tgcagacggc cctcacactg cctgtcctaa 960

aattcagcta ctccactgac ctgctgccac tgctcactga cctgggtctc gacgaatttc 1020

tggcagacac ggacctgacc aagatcacgt ctcaggcggc gaagctcggc agcctcaatc 1080

ataaggttgt catggagatg gccccagagg gcacccagta tgccagctcc ctccccgcct 1140

ccacacccct ttcgtactgc gtggaccatc ccttcctgtt cctggtgagg gatgaggcct 1200

cgggagcact gctctttatt ggcaaggtgg tcaacccacg caatctgagg atataaacac 1260

agacacacac tgccttctaa gcaggtccta ggaggggatc agccatcgtt aagcttaagc 1320

ttctgtgtgt cataaatgca caatatgaga gggtggataa gcagctagat ttacccattg 1380

atcatataat acagtttctt aatcatgtat ggaaaccatg cataacattc agactaaaag 1440

ttcagaccaa aagtctgaac actcacaact gatagtctca agttgttttc agggaaaata 1500

atttgtgatt gaaaagtaca gctctcataa tttttaaata gaggcacatt ctttaacccc 1560

aaaaatactc atcataatat tgtcaattgc gatgcaagaa ataaacattg aagttaagtc 1620

tttctgtttg tctgtctgac tccatagatg gaattgtata actttatcca gttgacatac 1680

aatagctgct tccagtaaag ggttgggtta ttttggaaag aaattggact cttggatgct 1740

ctttccttag ctattgtgct gttaaacaaa attaaaggac taacacaaaa aaaaaaaaaa 1800

aaaaaaaaga 1810

<210> 38

<211> 405
<212> PRT
<213> Salmo salar

<400> 38

```
Met Leu Arg Thr Thr Leu Leu Leu Cys Leu Gly Ala Leu Leu Ser Leu
1               5                  10                  15

Ser Tyr Ala Gln Leu Leu Glu Thr Glu Ala Ala Gly Gly Glu Glu Glu
            20                  25                  30

Ala Val Glu Leu Phe Thr Thr Pro Arg Ala Lys Met Ala Ala Ala Thr
        35                  40                  45

Ser Asp Phe Gly Tyr Asn Leu Phe Arg Ala Leu Ala Gly Arg Asn Pro
    50                  55                  60

Asn Thr Asn Val Phe Leu Ala Pro Ile Ser Ile Ser Ala Val Leu Thr
65                  70                  75                  80

Gln Leu Ser Met Gly Ala Ser Pro Asp Arg Ser Glu Arg Trp Leu Tyr
                85                  90                  95

Arg Ala Leu Arg Tyr His Thr Leu Gln Asp Pro Gln Leu His Asp Thr
            100                 105                 110

Leu Arg Asp Leu Leu Ala Ser Leu Arg Ala Pro Gly Lys Gly Leu Ser
        115                 120                 125

Ile Ala Ala Arg Val Tyr Leu Ala Arg Arg Leu Arg Leu Lys Gln Glu
    130                 135                 140

Tyr Phe Gly Val Val Glu Lys Gln Tyr Gly Val Arg Pro Lys Ala Leu
145                 150                 155                 160

Met Gly Gly Ala Lys Asp Val Asn Glu Ile Asn Asp Trp Val Lys Gln
                165                 170                 175

Gln Thr Gly Gly Lys Val Asp Arg Phe Met Ser Lys Pro Leu Gly Arg
            180                 185                 190

Asn Ser Gly Val Val Pro Leu Gly Ala Ala Tyr Phe Lys Val Lys Trp
        195                 200                 205

Met Thr Arg Phe Ser Gln Ser Gly Val Met Glu Asp Phe Gln Leu Val
    210                 215                 220

Gly Glu Ala Pro Ala Arg Ile Ser Met Met Gln Gln Asp Asn Tyr Pro
```

```
225                 230                 235                 240

Val Lys Met Gly Val Asp Pro Asp Leu Gly Cys Thr Ile Ala Gln Ile
                245                 250                 255

Gln Met Gln Asp Asp Val Ser Met Phe Val Phe Leu Pro Asp Asp Val
            260                 265                 270

Thr Gln Asn Met Thr Leu Val Glu Glu Ser Leu Thr Ala Glu Phe Val
        275                 280                 285

Gln Asp Leu Ser Met Thr Leu His Pro Val Gln Thr Ala Leu Thr Leu
    290                 295                 300

Pro Val Leu Lys Phe Ser Tyr Ser Thr Asp Leu Leu Pro Leu Leu Thr
305                 310                 315                 320

Asp Leu Gly Leu Asp Glu Phe Leu Ala Asp Thr Asp Leu Thr Lys Ile
                325                 330                 335

Thr Ser Gln Ala Ala Lys Leu Gly Ser Leu Asn His Lys Val Val Met
            340                 345                 350

Glu Met Ala Pro Glu Gly Thr Gln Tyr Ala Ser Ser Leu Pro Ala Ser
        355                 360                 365

Thr Pro Leu Ser Tyr Cys Val Asp His Pro Phe Leu Phe Leu Val Arg
    370                 375                 380

Asp Glu Ala Ser Gly Ala Leu Leu Phe Ile Gly Lys Val Val Asn Pro
385                 390                 395                 400

Arg Asn Leu Arg Ile
                405
```

<210> 39
<211> 1422
<212> DNA
<213> Ovis aries

<400> 39

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tccctggccc ctgagagcac aggggcaccc gtggaggaag aggatccctt cttcaaggtc 180

cccgtgaaca agctggcggc agccgtctcc aacttcggct acgacctgta ccgcgtgaga 240

tctggcgaga gccccaccac caacgtgctg ctgtctccgc tcagcgtggc cacggcgctc 300

tctgccctgt cgctgggtgc ggaacagcgg acagaatcca gcattcaccg ggctctgtac 360

tacgacctga tcagtaaccc agacatccac ggcacctaca aggacctcct tgcctccgtc 420

actgcccccc agaagaacct taaaagtgct tcccggatta tctttgagag gaagctgcgg 480

ataaaagcca gcttcgtccc acccctcgag aagtcatatg ggaccaggcc cagaatcctg 540

accggcaact ctcgaataga ccttcaggag attaacaact gggtgcaggc ccagatgaaa 600

gggaaaattg ctagatccac acgggaaata cccagtggaa tcagcattct ccttcttggt 660

gtggcttact tcaaggggca gtgggtaaca aagtttgact ccaggaagac ttccctggag 720

gatttccact tggatgaggg gaggaccgtg aaagttccca tgatgtcaga ccctaaggcc 780

gttttacggt acggcttgga ttctgatctc aactgcaaga tcgcccagct gcccttgacc 840

gggagcacaa gtatcatctt cttcctgcct cagaaagtga cccagaactt gaccttgata 900

gaagagagcc tcacctctga gttcattcat gacatagacc gagaactgaa gactgttcag 960

gcagtcctga ccattcccaa gctgaagctg agttatgaag gcgaactcac gaagtctgtg 1020

caggagctga agctacaatc cctgtttgat gcaccagact ttagcaagat cacaggcaaa 1080

cctatcaaac ttactcaagt ggaacatcgc atcggattcg agtggaatga ggatggggcg 1140

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cttaaccaac ctttcatctt tgtactgagg gacacagaca caggggccct tctcttcata 1260

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gaaaaaaaca ctagcgggat ggcagattat atattatatg aaggctgccc ctacgtttca 1380

atgtatactt tgcaataaaa gtgctttctc cttaaaaaaa aa 1422

<210> 40
<211> 416
<212> PRT
<213> Ovis aries

<400> 40

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Met Gln Ala Leu Val Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly Phe
1               5                  10                  15

Gly His Cys Gln Asn Ala Gly Pro Glu Ala Gly Ser Leu Ala Pro Glu
            20                  25                  30

Ser Thr Gly Ala Pro Val Glu Glu Glu Asp Pro Phe Phe Lys Val Pro
        35                  40                  45

Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu Tyr
    50                  55                  60

Arg Val Arg Ser Gly Glu Ser Pro Thr Thr Asn Val Leu Leu Ser Pro
```

65 70 75 80

Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu Gln
85 90 95

Arg Thr Glu Ser Ser Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser
100 105 110

Asn Pro Asp Ile His Gly Thr Tyr Lys Asp Leu Leu Ala Ser Val Thr
115 120 125

Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Ile Phe Glu Arg
130 135 140

Lys Leu Arg Ile Lys Ala Ser Phe Val Pro Pro Leu Glu Lys Ser Tyr
145 150 155 160

Gly Thr Arg Pro Arg Ile Leu Thr Gly Asn Ser Arg Ile Asp Leu Gln
165 170 175

Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Ile Ala Arg
180 185 190

Ser Thr Arg Glu Ile Pro Ser Gly Ile Ser Ile Leu Leu Leu Gly Val
195 200 205

Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr
210 215 220

Ser Leu Glu Asp Phe His Leu Asp Glu Gly Arg Thr Val Lys Val Pro
225 230 235 240

Met Met Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp Ser Asp
245 250 255

Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Thr Ser Ile
260 265 270

Ile Phe Phe Leu Pro Gln Lys Val Thr Gln Asn Leu Thr Leu Ile Glu
275 280 285

Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys
290 295 300

Thr Val Gln Ala Val Leu Thr Ile Pro Lys Leu Lys Leu Ser Tyr Glu
305 310 315 320

```
Gly Glu Leu Thr Lys Ser Val Gln Glu Leu Lys Leu Gln Ser Leu Phe
                325                 330                 335

Asp Ala Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr
            340                 345                 350

Gln Val Glu His Arg Ile Gly Phe Glu Trp Asn Glu Asp Gly Ala Gly
        355                 360                 365

Thr Asn Ser Ser Pro Gly Val Gln Pro Ala Arg Leu Thr Phe Pro Leu
    370                 375                 380

Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp
385                 390                 395                 400

Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Thr
                405                 410                 415
```

<210> 41
<211> 1465
<212> DNA
<213> Cavia porcellus

<400> 41

gtgcagactg agcaggacct gaactggagt acggctggga gcagagctgc agggaaccac 60

aggttcagga tgcaggtcct tgtgctactc ctctggaccg gagccctgct agggcgtggc 120

agctgccagg acatcgccag caacccggag gactccccgt cccctgaaag cacaggggag 180

ccagtggagg aggaggaccc cttcttcaag gtccctgtga acaagctggc tgcagccatc 240

tccaactttg gctacgacct ataccgggtg agatccatcg agagccccac caccaatgtg 300

ctgctgtccc ccctcagcgt ggccaccgcc ctctctgccc tttcgctggg ggcggaacag 360

cgaacagaag ccaccattca tcgggctctc tactatgaca tgatcagcaa ccctgacatc 420

cacagcacct acaaggagct cctggccact gtcaccgccc cgcagaagaa cctgaagagt 480

gcttcgagga ttgtctttga gaggaagctg cgcataaaat ccagccttgt cgcactactg 540

gaaaagtcat attcgaccag gcccagaatc ctgactggca accctcgcat tgaccttcaa 600

gagattagca actgggtgca ggcccagatg aaagggaaaa tcaccaggtc tacgagggaa 660

gtgcccagtg gcatcagcat tctccttctc ggtgtggctt acttcaaggg gcagtgggtc 720

acaaaatttg actccagaaa gacttctctc caggatttcc acttggatga ggagaggact 780

gtaaaagttc ccatgatgtc agaccccaag gccatcatac gctatggcct ggatactgat 840

ctcaactgca agattgccca gctgcccttg actggaagca tgagtatcat cttcttcttg 900

cccatgaggg caacccagaa cttgaccatg atagaagaga gcctcacctc cgagtttgtt 960

catgacataa accgagaact gaaggctgtc caagcggttc tcagcatccc caggctgaag 1020

ctgagtttcg aaggcgaact taccaagtcc ctgcaggaga tgaagctgca ttccttgttt 1080

gagtcccccg actttagcaa gatcacaggc aaacctatca agctgactca agtggaacac 1140

cgggctggtt tcgagtggaa tgaggagggg gcgccaggaa ccagcaccaa ctcagacctc 1200

cagcctactg gcttcacatt ctctctggac tatcacctga accagccgtt catcttcgtc 1260

ctgagagaca cggacacggg ggcccttctc ttcataggca aaattctgga ccccagaagt 1320

acttaatgct ccagtttaat gttctactac tctagaaaga aaccccagaa ggatggcagt 1380

ttatacatta caggggggca gcccccacag tttcagtgta tactttgcaa taaaagagct 1440

ttatccttaa aaaaaaaaaa aaaaa 1465

<210> 42
<211> 418
<212> PRT
<213> Cavia porcellus

<400> 42

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Met Gln Val Leu Val Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly Arg
1               5                  10                  15

Gly Ser Cys Gln Asp Ile Ala Ser Asn Pro Glu Asp Ser Pro Ser Pro
            20                  25                  30

Glu Ser Thr Gly Glu Pro Val Glu Glu Glu Asp Pro Phe Phe Lys Val
        35                  40                  45

Pro Val Asn Lys Leu Ala Ala Ala Ile Ser Asn Phe Gly Tyr Asp Leu
    50                  55                  60

Tyr Arg Val Arg Ser Ile Glu Ser Pro Thr Thr Asn Val Leu Leu Ser
65                  70                  75                  80

Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu
                85                  90                  95

Gln Arg Thr Glu Ala Thr Ile His Arg Ala Leu Tyr Tyr Asp Met Ile
            100                 105                 110

Ser Asn Pro Asp Ile His Ser Thr Tyr Lys Glu Leu Leu Ala Thr Val
        115                 120                 125

Thr Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe Glu
    130                 135                 140

Arg Lys Leu Arg Ile Lys Ser Ser Leu Val Ala Leu Leu Glu Lys Ser
145                 150                 155                 160
```

```
Tyr Ser Thr Arg Pro Arg Ile Leu Thr Gly Asn Pro Arg Ile Asp Leu
                165                 170                 175

Gln Glu Ile Ser Asn Trp Val Gln Ala Gln Met Lys Gly Lys Ile Thr
            180                 185                 190

Arg Ser Thr Arg Glu Val Pro Ser Gly Ile Ser Ile Leu Leu Leu Gly
        195                 200                 205

Val Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys
    210                 215                 220

Thr Ser Leu Gln Asp Phe His Leu Asp Glu Glu Arg Thr Val Lys Val
225                 230                 235                 240

Pro Met Met Ser Asp Pro Lys Ala Ile Ile Arg Tyr Gly Leu Asp Thr
                245                 250                 255

Asp Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met Ser
            260                 265                 270

Ile Ile Phe Phe Leu Pro Met Arg Ala Thr Gln Asn Leu Thr Met Ile
        275                 280                 285

Glu Glu Ser Leu Thr Ser Glu Phe Val His Asp Ile Asn Arg Glu Leu
    290                 295                 300

Lys Ala Val Gln Ala Val Leu Ser Ile Pro Arg Leu Lys Leu Ser Phe
305                 310                 315                 320

Glu Gly Glu Leu Thr Lys Ser Leu Gln Glu Met Lys Leu His Ser Leu
                325                 330                 335

Phe Glu Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu
            340                 345                 350

Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Glu Gly Ala
        355                 360                 365

Pro Gly Thr Ser Thr Asn Ser Asp Leu Gln Pro Thr Gly Phe Thr Phe
    370                 375                 380

Ser Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp
385                 390                 395                 400

Thr Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg
```

405 410 415

Ser Thr

<210> 43
<211> 1408
<212> DNA
<213> Bos taurus

<400> 43

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tgcttgggtt tggccgctgc cagaacgccg gccaggaggc gggctctctg acccctgaga 120

gcacgggggc accagtggag gaagaggatc ccttcttcaa ggtccctgtg aacaagctgg 180

cggcagcggt ctccaacttc ggctacgacc tgtaccgcgt gagatccggt gagagcccca 240

ccgccaatgt gctgctgtct ccgctcagcg tggccacggc gctctctgcc ctgtcgctgg 300

gtgcggaaca gcggacagaa tccaacattc accgggctct gtactacgac ctgatcagta 360

acccagacat ccacggcacc tacaaggacc tccttgcctc cgtcaccgcc ccccagaaga 420

accttaagag tgcttcccgg attatctttg agaggaagct gcggataaaa gccagcttca 480

tcccacccct ggagaagtca tatgggacca ggcccagaat cctgaccggc aactctcgag 540

tagaccttca ggagattaac aactgggtgc aggcccagat gaaagggaaa gtcgctaggt 600

ccacgaggga gatgcccagt gagatcagca ttttcctcct gggcgtggct tacttcaagg 660

ggcagtgggt aacaaagttt gactccagaa aaacttccct ggaggatttc tacttggatg 720

aggagaggac cgtgaaagtc cccatgatgt cagaccctca ggccgtttta cggtacggct 780

tggattctga tctcaactgc aagatcgccc agctgccctt gaccgggagc acaagtatca 840

tcttcttcct gcctcagaaa gtgacccaga acttgacctt gatagaagag agcctcacct 900

ctgagttcat tcatgacata gaccgagaac tgaagactgt tcaggcggtc ctgaccattc 960

ccaagctgaa gctgagttat gaaggcgaac tcacgaagtc cgtgcaggag ctgaagctgc 1020

aatccctgtt tgatgcacca gactttagca agatcacagg caaacctatc aaacttactc 1080

aagtggaaca tcgcgtcgga tttgagtgga atgaggatgg ggcgggtact aactccagcc 1140

caggggtcca gcctgcccgc ctcaccttcc ctctggacta tcaccttaac caacctttca 1200

tctttgtact gagggacaca gacacagggg cccttctctt cataggcaaa attctggacc 1260

ccaggggcac ttagtactcc aactaaatgt tcaaataccc cagaagaaaa aaacactaga 1320

gggatggcag attatatatt atacgaaggc tgcccctaca tttcaatgta tactttgcaa 1380

taaaagtgct ttatccttaa aaaaaaaa 1408

<210> 44
<211> 416
<212> PRT
<213> Bos taurus

<400> 44

```
Met Gln Ala Leu Val Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly Phe
1               5                  10                  15

Gly Arg Cys Gln Asn Ala Gly Gln Glu Ala Gly Ser Leu Thr Pro Glu
            20                  25                  30

Ser Thr Gly Ala Pro Val Glu Glu Glu Asp Pro Phe Phe Lys Val Pro
        35                  40                  45

Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu Tyr
    50                  55                  60

Arg Val Arg Ser Gly Glu Ser Pro Thr Ala Asn Val Leu Leu Ser Pro
65                  70                  75                  80

Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu Gln
                85                  90                  95

Arg Thr Glu Ser Asn Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser
            100                 105                 110

Asn Pro Asp Ile His Gly Thr Tyr Lys Asp Leu Leu Ala Ser Val Thr
        115                 120                 125

Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Ile Phe Glu Arg
    130                 135                 140

Lys Leu Arg Ile Lys Ala Ser Phe Ile Pro Pro Leu Glu Lys Ser Tyr
145                 150                 155                 160

Gly Thr Arg Pro Arg Ile Leu Thr Gly Asn Ser Arg Val Asp Leu Gln
                165                 170                 175

Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Val Ala Arg
            180                 185                 190

Ser Thr Arg Glu Met Pro Ser Glu Ile Ser Ile Phe Leu Leu Gly Val
        195                 200                 205

Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr
    210                 215                 220

Ser Leu Glu Asp Phe Tyr Leu Asp Glu Glu Arg Thr Val Lys Val Pro
```

225 230 235 240

Met Met Ser Asp Pro Gln Ala Val Leu Arg Tyr Gly Leu Asp Ser Asp
245 250 255

Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Thr Ser Ile
260 265 270

Ile Phe Phe Leu Pro Gln Lys Val Thr Gln Asn Leu Thr Leu Ile Glu
275 280 285

Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys
290 295 300

Thr Val Gln Ala Val Leu Thr Ile Pro Lys Leu Lys Leu Ser Tyr Glu
305 310 315 320

Gly Glu Leu Thr Lys Ser Val Gln Glu Leu Lys Leu Gln Ser Leu Phe
325 330 335

Asp Ala Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr
340 345 350

Gln Val Glu His Arg Val Gly Phe Glu Trp Asn Glu Asp Gly Ala Gly
355 360 365

Thr Asn Ser Ser Pro Gly Val Gln Pro Ala Arg Leu Thr Phe Pro Leu
370 375 380

Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp
385 390 395 400

Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Thr
405 410 415

<210> 45
<211> 1418
<212> DNA
<213> Sus scrofa

<400> 45

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ccctcgtgct actcctctgg actggagccc tcctcgggtc tggcagctgc cagaacgctg 120

gcccggagga gggctccccg gcccctgaca cggtgggggc gccagtggag gaggaggatc 180

ccttcttcaa ggtccctgtg aacaagctgg cggcggccgt ctccaacttt ggttacgacc 240

tgtaccgagt gagatccagc gagagcccca ccgccaacgt gctcctgtct cccctcagcg 300

tggccacggc gctctctgcc ctgtctctgg gagccgaaca gcggacagaa tccagcctcc 360

accgggctct ctactatgac ctgatcagca acccggacct ccacggcacc tacaaggagc 420

tccttgctgc cgtcactgcc ccccagaaga acctcaagag tgcttcccgg atcatctttg 480

agaagaagct gcggataaaa gccagctttg ttgcacccct ggaaaagtca tacgggacca 540

ggcccagaat tctgaccggc aactcccgct tggaccttca ggaggttaac aactgggtgc 600

aggctcagac gaaagggaaa gtcgccaggt ccacgcggga actgcccggc gaaatcagca 660

tcctccttct tggtgtggct tacttcaagg ggcagtgggt aaccaagttt gactccagga 720

agacgtcgct ggaggatttc cacttggatg aggagagaac cgtgaaggtg cccatgatgt 780

cagaccctaa ggccgtttta cgctacggct tggattctga tctcaactgc aagattgccc 840

agctgccctt gaccggaagc atgagtatca tcttcttcct gcctctgaaa gtgacccaga 900

acctgaccat gatagaagag agcctcacct ctgagttcat tcacgacata gaccgagaac 960

tgaagacggt tcaagcggtc ctgaccgtcc ccaagctgaa gctgagttac gaaggcgaac 1020

tcacgaagtc tgtgcaggaa ctgaagctgc aatccttgtt tgattcacca gactttagca 1080

agatcacggg caaacctatc aaacttactc aagtggaaca tcgcattggc tttgagtgga 1140

acgaggatgg gggaagcgcc acctccagcc cagggccccg cctcaccttc cccctggact 1200

atcaccttaa ccagcctttc atctttgtac tgagggacac agacacagga gcccttctct 1260

tcataggcaa gattctggac cccaggagca cttaatgctc tagtttaatg ttcaaatatc 1320

ccagaagaag aaaactctag acagatggca gattatatat tacacgaaag ctgcacatat 1380

gtttcaatgt atactttgca ataaaagtgc tttatccc 1418

<210> 46
<211> 413
<212> PRT
<213> Sus scrofa

<400> 46

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Met Gln Ala Leu Val Leu Leu Leu Trp Thr Gly Ala Leu Leu Gly Ser
1               5                  10                  15

Gly Ser Cys Gln Asn Ala Gly Pro Glu Glu Gly Ser Pro Ala Pro Asp
            20                  25                  30

Thr Val Gly Ala Pro Val Glu Glu Glu Asp Pro Phe Phe Lys Val Pro
        35                  40                  45

Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu Tyr
    50                  55                  60

Arg Val Arg Ser Ser Glu Ser Pro Thr Ala Asn Val Leu Leu Ser Pro
```

65 70 75 80

Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu Gln
85 90 95

Arg Thr Glu Ser Ser Leu His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser
100 105 110

Asn Pro Asp Leu His Gly Thr Tyr Lys Glu Leu Leu Ala Ala Val Thr
115 120 125

Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Ile Phe Glu Lys
130 135 140

Lys Leu Arg Ile Lys Ala Ser Phe Val Ala Pro Leu Glu Lys Ser Tyr
145 150 155 160

Gly Thr Arg Pro Arg Ile Leu Thr Gly Asn Ser Arg Leu Asp Leu Gln
165 170 175

Glu Val Asn Asn Trp Val Gln Ala Gln Thr Lys Gly Lys Val Ala Arg
180 185 190

Ser Thr Arg Glu Leu Pro Gly Glu Ile Ser Ile Leu Leu Leu Gly Val
195 200 205

Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr
210 215 220

Ser Leu Glu Asp Phe His Leu Asp Glu Glu Arg Thr Val Lys Val Pro
225 230 235 240

Met Met Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp Ser Asp
245 250 255

Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met Ser Ile
260 265 270

Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Met Ile Glu
275 280 285

Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys
290 295 300

Thr Val Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser Tyr Glu
305 310 315 320

Gly Glu Leu Thr Lys Ser Val Gln Glu Leu Lys Leu Gln Ser Leu Phe
325 330 335

Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr
340 345 350

Gln Val Glu His Arg Ile Gly Phe Glu Trp Asn Glu Asp Gly Gly Ser
355 360 365

Ala Thr Ser Ser Pro Gly Pro Arg Leu Thr Phe Pro Leu Asp Tyr His
370 375 380

Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp Thr Gly Ala
385 390 395 400

Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Ser Thr
405 410

<210> 47
<211> 1317
<212> DNA
<213> Ornithorhynchus anatinus

<400> 47

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acaatgcagc cctttgcggt actcctgtgg gtgggagtcc tcatcggctc cagtaagtcc 120

caggatgccg ctgggcctga ggaatctcca gctcccgacg ccacggggac tgcggtggtg 180

gaggaggagg acccctttctt caaggtccct gtgaacaagc tggcagccgc cgtctccaac 240

tttggctacg acctgtatcg ccagaaatcc agctcgagcc ccaccaccaa tgtgctgctg 300

tcccctctca gtgtggccac cgctctctct agcctctcct tgggtgctgg gccccggacg 360

gaaagcctca tacaccgggc tctttattat gacttgattc acaacccgga catccacggc 420

acttacaagg aacttctcgc tacagtcacc gctccgcaaa agaacctgaa gactgcttcc 480

cggcttgtct tggagagaaa gctgcggata aaagctggat tcgttgggct gctggaaaag 540

tcgtatggat ccaggccgaa gattctgacg ggcaacactc ggactgacct tcacgaaatg 600

aacaactgga tgcagaccca gactaagggg aagatgggcc ggacgctgaa ggagctgccc 660

agtggaatta gcgttcttct tcttgggata gcttacttca aagggcagtg ggtgactaag 720

tttgatccca agaagacttc cctgcaggac ttccacttgg atgaagaccg aactgtaaaa 780

gtccccatga tgtcagatcc caaggctatc atacgctacg gcctggactc cgacctcaac 840

tgcaagattg cccagctgcc cctggaggga agcatgagcg tcattttctt cctgccgctg 900

aaagcaaccc agaacctgac gctcatagag gagagtctca cctcagagtt cattcacgac 960

attgacagag agctgaagac catccaggcg gtgctaactg tacccaagct tcagctcagc 1020

ttcgagggag aagtgtccaa aacatttcag gagataaagc ttcagtctct cttcaactcc 1080

ccggatctca gcaagatcac gcccagaccc atcaagctca ctcacgtggt gcaccggtca 1140

tctctggaat ggagtgagga tggggtgggg gacgccccca gccccgcgct actgcccgct 1200

cgactgacct tccccctgga ctaccacctc aaccagcctt tcatctttgt cttgcgggac 1260

actgacacgg gcacccttct cttcattggc aaaatcctgg accccagggg caactga 1317

<210> 48
<211> 417
<212> PRT
<213> Ornithorhynchus anatinus

<400> 48

```
Met Gln Pro Phe Ala Val Leu Leu Trp Val Gly Val Leu Ile Gly Ser
1               5                  10                  15

Ser Lys Ser Gln Asp Ala Ala Gly Pro Glu Glu Ser Pro Ala Pro Asp
            20                  25                  30

Ala Thr Gly Thr Ala Val Val Glu Glu Glu Asp Pro Phe Phe Lys Val
        35                  40                  45

Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu
    50                  55                  60

Tyr Arg Gln Lys Ser Ser Ser Ser Pro Thr Thr Asn Val Leu Leu Ser
65                  70                  75                  80

Pro Leu Ser Val Ala Thr Ala Leu Ser Ser Leu Ser Leu Gly Ala Gly
                85                  90                  95

Pro Arg Thr Glu Ser Leu Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile
            100                 105                 110

His Asn Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Ala Thr Val
        115                 120                 125

Thr Ala Pro Gln Lys Asn Leu Lys Thr Ala Ser Arg Leu Val Leu Glu
    130                 135                 140

Arg Lys Leu Arg Ile Lys Ala Gly Phe Val Gly Leu Leu Glu Lys Ser
145                 150                 155                 160

Tyr Gly Ser Arg Pro Lys Ile Leu Thr Gly Asn Thr Arg Thr Asp Leu
                165                 170                 175
```

```
His Glu Met Asn Asn Trp Met Gln Thr Gln Thr Lys Gly Lys Met Gly
            180                 185                 190

Arg Thr Leu Lys Glu Leu Pro Ser Gly Ile Ser Val Leu Leu Leu Gly
        195                 200                 205

Ile Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Pro Lys Lys
    210                 215                 220

Thr Ser Leu Gln Asp Phe His Leu Asp Glu Asp Arg Thr Val Lys Val
225                 230                 235                 240

Pro Met Met Ser Asp Pro Lys Ala Ile Ile Arg Tyr Gly Leu Asp Ser
                245                 250                 255

Asp Leu Asn Cys Lys Ile Ala Gln Leu Pro Leu Glu Gly Ser Met Ser
            260                 265                 270

Val Ile Phe Phe Leu Pro Leu Lys Ala Thr Gln Asn Leu Thr Leu Ile
        275                 280                 285

Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu
    290                 295                 300

Lys Thr Ile Gln Ala Val Leu Thr Val Pro Lys Leu Gln Leu Ser Phe
305                 310                 315                 320

Glu Gly Glu Val Ser Lys Thr Phe Gln Glu Ile Lys Leu Gln Ser Leu
                325                 330                 335

Phe Asn Ser Pro Asp Leu Ser Lys Ile Thr Pro Arg Pro Ile Lys Leu
            340                 345                 350

Thr His Val Val His Arg Ser Ser Leu Glu Trp Ser Glu Asp Gly Val
        355                 360                 365

Gly Asp Ala Pro Ser Pro Ala Leu Leu Pro Ala Arg Leu Thr Phe Pro
    370                 375                 380

Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr
385                 390                 395                 400

Asp Thr Gly Thr Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly
                405                 410                 415

Asn
```

<210> 49
<211> 1484
<212> DNA
<213> Canis lupus familiaris

<400> 49

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cctctggacc ggagccctcc tggggcacag cagctgccag aacgatgcgg gcggccccca 180

aggactctcc agctcccgac gcgacagggg tgcccgtgga ggaggaggac cccttcttca 240

gggtccccgt gaataagctg gcagcagcca tctccaactt cggctatgac ctgtaccgtg 300

taaggtccag cttcagccct gctgccaatg tgctgctgtc accactcagc gtggccaccg 360

cactctctgc gctctcgctg ggagcggaac agcggacaga atccaccatt caccgggctc 420

tctactacga cctgatcagc aacccggaca tccacagcac ctataaggag ctccttgcct 480

ctgtcactgc cccggagaag aacttcaaga gtgcttcccg gattgtcttt gagaggaagc 540

tgcggataaa atccagcttt gttgcaccac tggagaagtc ctatagcacc aggcccagaa 600

tcctgaccgg caaccctcgc ctggaccttc aggaggttaa caactgggtg caggcccaga 660

tgaaagggaa aattgctaga tccacacggg aaatacccag tggaatcagc attctccttc 720

ttggtgtggc ttacttcaag gggcagtggg taacaaagtt tgactccaga aagacttccc 780

tcgaggattt ccacttggat gaggagagga ctgtgaaagt ccccatgatg tcagacccta 840

aggccatctt acgctatggc ttggactctg atctcagctg taagattgcc cagctgccct 900

tgaccggcag catgagtatc atctttttcc tgcctctgaa agtaacccag aacttgacca 960

tgatagaaga gagcctcacc tctgagttca ttcatgacat agaccgagag ctgaagacaa 1020

ttcaagcagt cctgaccatc cccaagctga agctgagtta tgaaggcgaa gtcacgaagt 1080

ccctgcagga aatgaaactg caatccttgt ttgattcacc agacttcagc aagatcacag 1140

gcaaacctat taaacttacc caagtggaac atcgagctgg cttcgagtgg aacgaggatg 1200

gggcaggcac caccccagc ccggggctcc agcctacccg cctcaccttt cctctggatt 1260

atcacctgaa ccgacctttc atctttgtgc tgagagacac agacacaggg gcccttctct 1320

tcataggcaa aatcctggac cccaggggca tttaatgctc cggtttttaa tgttccaata 1380

ccctagaaga acaaaaccct caacggatgg cagatgacat attacatgaa ggctgcccct 1440

acaatggttt cagtgtatac tttgcaataa aagtgcttta tcct 1484

<210> 50
<211> 396
<212> PRT
<213> Canis lupus familiaris

<400> 50

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Met Arg Ala Ala Pro Lys Asp Ser Pro Ala Pro Asp Ala Thr Gly Val
1               5                  10                  15

Pro Val Glu Glu Glu Asp Pro Phe Phe Arg Val Pro Val Asn Lys Leu
            20                  25                  30

Ala Ala Ala Ile Ser Asn Phe Gly Tyr Asp Leu Tyr Arg Val Arg Ser
        35                  40                  45

Ser Phe Ser Pro Ala Ala Asn Val Leu Leu Ser Pro Leu Ser Val Ala
    50                  55                  60

Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu Gln Arg Thr Glu Ser
65                  70                  75                  80

Thr Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser Asn Pro Asp Ile
                85                  90                  95

His Ser Thr Tyr Lys Glu Leu Leu Ala Ser Val Thr Ala Pro Glu Lys
            100                 105                 110

Asn Phe Lys Ser Ala Ser Arg Ile Val Phe Glu Arg Lys Leu Arg Ile
        115                 120                 125

Lys Ser Ser Phe Val Ala Pro Leu Glu Lys Ser Tyr Ser Thr Arg Pro
    130                 135                 140

Arg Ile Leu Thr Gly Asn Pro Arg Leu Asp Leu Gln Glu Val Asn Asn
145                 150                 155                 160

Trp Val Gln Ala Gln Met Lys Gly Lys Ile Ala Arg Ser Thr Arg Glu
                165                 170                 175

Ile Pro Ser Gly Ile Ser Ile Leu Leu Leu Gly Val Ala Tyr Phe Lys
            180                 185                 190

Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr Ser Leu Glu Asp
        195                 200                 205

Phe His Leu Asp Glu Glu Arg Thr Val Lys Val Pro Met Met Ser Asp
    210                 215                 220

Pro Lys Ala Ile Leu Arg Tyr Gly Leu Asp Ser Asp Leu Ser Cys Lys
225                 230                 235                 240

Ile Ala Gln Leu Pro Leu Thr Gly Ser Met Ser Ile Ile Phe Phe Leu
```

245 250 255

Pro Leu Lys Val Thr Gln Asn Leu Thr Met Ile Glu Glu Ser Leu Thr
260 265 270

Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys Thr Ile Gln Ala
275 280 285

Val Leu Thr Ile Pro Lys Leu Lys Leu Ser Tyr Glu Gly Glu Val Thr
290 295 300

Lys Ser Leu Gln Glu Met Lys Leu Gln Ser Leu Phe Asp Ser Pro Asp
305 310 315 320

Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr Gln Val Glu His
325 330 335

Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly Ala Gly Thr Thr Pro Ser
340 345 350

Pro Gly Leu Gln Pro Thr Arg Leu Thr Phe Pro Leu Asp Tyr His Leu
355 360 365

Asn Arg Pro Phe Ile Phe Val Leu Arg Asp Thr Asp Thr Gly Ala Leu
370 375 380

Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Ile
385 390 395

<210> 51
<211> 1579
<212> DNA
<213> Macaca fascicularis

<400> 51

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<210> 52
<211> 418
<212> PRT
<213> Macaca fascicularis

<400> 52

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Met Gln Ala Leu Val Leu Phe Leu Cys Phe Ala Ala Leu Leu Gly His
1               5                  10                  15

Ser Ser Cys Gln Ser Leu Ala Ser Gly Pro Glu Glu Gly Ser Pro Asp
            20                  25                  30

Pro Asp Ser Thr Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys
        35                  40                  45

Val Pro Val Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp
    50                  55                  60

Leu Tyr Arg Val Arg Ser Ser Met Ser Pro Thr Thr Asn Val Leu Leu
65                  70                  75                  80
```

```
Ser Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala
                85                  90                  95

Glu Gln Arg Thr Glu Ser Val Ile His Arg Ala Leu Tyr Tyr Asp Leu
            100                 105                 110

Ile Ser Ser Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Gly Thr
        115                 120                 125

Val Thr Ala Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe
    130                 135                 140

Glu Lys Lys Leu Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys
145                 150                 155                 160

Ser Tyr Gly Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp
                165                 170                 175

Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu
            180                 185                 190

Ala Arg Ser Thr Lys Glu Leu Pro Asp Glu Ile Ser Ile Leu Leu Leu
        195                 200                 205

Gly Val Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Pro Arg
    210                 215                 220

Lys Thr Ser Leu Glu Asp Phe His Leu Asp Glu Glu Arg Thr Val Arg
225                 230                 235                 240

Val Pro Met Met Ser Asp Pro Lys Ala Ile Leu Arg Tyr Gly Leu Asp
                245                 250                 255

Ser Asp Leu Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
            260                 265                 270

Ser Ile Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu
        275                 280                 285

Ile Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu
    290                 295                 300

Leu Lys Thr Val Gln Ala Val Leu Thr Leu Pro Lys Leu Lys Leu Ser
305                 310                 315                 320

Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Thr Lys Leu Gln Ser
                325                 330                 335
```

```
Leu Phe Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys
            340                 345                 350

Leu Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly
        355                 360                 365

Ala Gly Ala Thr Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe
    370                 375                 380

Leu Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp
385                 390                 395                 400

Thr Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg
                405                 410                 415

Gly Thr
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<210> 53
<211> 1935
<212> DNA
<213> Pan troglodytes

<400> 53

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cattggagcc ctcctcgggc acagcagctg ccagaaccct gccagccccc cggaggagag    180
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cagtccctgt gcatctctgc gagtccctga actcaaaccc aagacttcct gtctcctgcc    360
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tgaaagggaa gctcgccagg tccacaaagg aaattcccga tgagatcagc attctccttc    900
tcggtgtggc gcacttcaag gggcagtggg taacaaagtt tgactccaga aagacttccc    960
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agcaacacat ggaca 1935

<210> 54
<211> 415
<212> PRT
<213> Pan troglodytes

<400> 54

Met Arg Arg Gln Ser Val Pro Val His Leu Cys Glu Ser Leu Asn Ser
1 5 10 15

Asn Pro Arg Leu Pro Val Ser Cys Gln Gly Ser Pro Asp Pro Asp Ser
20 25 30

Thr Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys Val Pro Val
35 40 45

Asn Lys Leu Ala Ala Ala Val Ser Asn Phe Gly Tyr Asp Leu Tyr Arg
50 55 60

Val Arg Ser Ser Met Ser Pro Thr Thr Asn Val Leu Leu Ser Pro Leu
65 70 75 80

```
Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala Glu Gln Arg
                85                  90                  95

Thr Glu Ser Ile Ile His Arg Ala Leu Tyr Tyr Asp Leu Ile Ser Ser
            100                 105                 110

Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Asp Thr Val Thr Ala
        115                 120                 125

Pro Gln Lys Asn Leu Lys Ser Ala Ser Arg Ile Val Phe Glu Lys Lys
    130                 135                 140

Leu Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys Ser Tyr Gly
145                 150                 155                 160

Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp Leu Gln Glu
                165                 170                 175

Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu Ala Arg Ser
            180                 185                 190

Thr Lys Glu Ile Pro Asp Glu Ile Ser Ile Leu Leu Leu Gly Val Ala
        195                 200                 205

His Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg Lys Thr Ser
    210                 215                 220

Leu Glu Asp Phe His Leu Asp Glu Glu Arg Thr Val Arg Val Pro Met
225                 230                 235                 240

Met Ser Asp Pro Lys Ala Val Leu Arg Tyr Gly Leu Asp Ser Asp Leu
                245                 250                 255

Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Thr Ser Ile Ile
            260                 265                 270

Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu Ile Glu Glu
        275                 280                 285

Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu Leu Lys Thr
    290                 295                 300

Val Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser Tyr Glu Gly
305                 310                 315                 320

Glu Val Thr Lys Ser Leu Gln Glu Met Lys Leu Gln Ser Leu Phe Asp
                325                 330                 335
```

Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys Leu Thr Gln
340 345 350

Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly Ala Gly Thr
355 360 365

Thr Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe Pro Leu Asp
370 375 380

Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp Thr
385 390 395 400

Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Thr
405 410 415

<210> 55
<211> 833
<212> DNA
<213> Macaca mulatta

<400> 55

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ctgcaggaga cgatggacta tcaccttaac cagcctttca tcttcgtcct gagggacacg 660

gacacagggg cccttctctt cattggcaag attctggacc ccagaggcac ctaataccct 720

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<210> 56
<211> 237
<212> PRT
<213> Macaca mulatta

<400> 56

```
Met Trp Gly Ser Ala Ala Pro Trp Pro Val Pro Gly Asp Ala Ser Arg
1               5                  10                  15

Ser Pro Glu Leu Arg Ile Lys Ser Ser Phe Val Ala Pro Leu Glu Lys
            20                  25                  30

Ser Tyr Gly Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp
        35                  40                  45

Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu
    50                  55                  60

Ala Arg Ser Thr Lys Glu Leu Pro Asp Glu Ile Ser Ile Leu Leu Leu
65                  70                  75                  80

Gly Val Ala Tyr Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Pro Arg
                85                  90                  95

Lys Thr Ser Leu Glu Asp Phe His Leu Asp Glu Glu Arg Thr Val Arg
            100                 105                 110

Val Pro Met Met Ser Asp Pro Lys Ala Ile Leu Arg Tyr Gly Leu Asp
        115                 120                 125

Ser Asp Leu Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
    130                 135                 140

Ser Ile Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu
145                 150                 155                 160

Ile Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu
                165                 170                 175

Leu Lys Thr Val Gln Ala Val Leu Thr Leu Pro Lys Leu Lys Leu Ser
            180                 185                 190

Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Thr Met Asp Tyr His
        195                 200                 205

Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp Thr Asp Thr Gly Ala
    210                 215                 220

Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg Gly Thr
225                 230                 235
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<210> 57
<211> 4645

<212> DNA
<213> Paralichthys olivaceus

<400> 57

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ttttcaattg tgtccgtccc tccatcgtcc ccctccctgt aggcctcact gattggatgg 3960

agaacccgca gctggagaag atctcaaccc aggctgccaa gctcaccagc gtcaatcaca 4020

aggtcatcat ggagacagca cctgaaggtg accagtaccc cggcgccatg tcaacaccca 4080

accacctgtc ataccgggtg gaccgcccct tcctctacct gatccgggac gaagcatcgg 4140

gggcgctgct cttcattggc agagtggtca accccaaaga cctgaggata taagacagat 4200

tcccataatg cattgccatt taacctcacc tcaaccctca ccccaaccct cacctcaacc 4260

ctcacctcaa ccctcacccc aaccctcacc tcaaccctca cctcaaccct caccccaacc 4320

ctcacctcac cctcacccca accctcacct caaacttcac cctagaacca agtctgagct 4380

tcaaatagca caaacaataa gacgccataa ttttctctaa actcaagctc tcttcatggt 4440

cctcttctca ggtcgtacga cagatttcag gtgtttgctc cacgtttgtg gcggcagatc 4500

tgtgaggacg tttgatttga tttttcttac ttttcatgtt gaaacaaaca cgttggtgtg 4560

atcatgttaa gatactgatg atacgaggaa agatgttaga aatattgtca tttgttttca 4620

aaggaataaa cacgacaatg aaagc 4645

<210> 58
<211> 403
<212> PRT
<213> Paralichthys olivaceus

<400> 58

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Met Lys Thr Thr Thr Phe Leu Leu Met Cys Gly Val Val Leu Ser Phe
1               5                  10                  15

Ser Gln Ala Gln Ser Glu Gly Glu Glu Thr Thr Val Glu Glu Glu His
            20                  25                  30

Val Glu Leu Phe Thr Thr Pro Thr Thr Arg Leu Ala Ala Ala Thr Ser
        35                  40                  45

Asp Phe Gly Tyr Asn Leu Phe Arg Ser Leu Ala Ser Arg Asp Thr Thr
    50                  55                  60

Thr Asn Val Phe Leu Ala Pro Ile Ser Val Ser Ala Ala Leu Thr Gln
65                  70                  75                  80

Leu Ser Met Gly Gly Ser Glu Leu Ala Glu Arg Gln Leu Phe Arg Ala
                85                  90                  95
```

```
Leu Arg Phe His Thr Leu Gln Asp Pro Gln Leu His Asn Thr Leu Lys
            100                 105                 110

Asp Leu Leu Ala Ser Leu Arg Ser Pro Gly Lys Gly Leu Ser Ile Ala
        115                 120                 125

Ala Arg Leu Tyr Leu Ala Arg Arg Leu Arg Leu Asn Gln Glu Phe Leu
    130                 135                 140

Ala Leu Val Glu Gln Gln Tyr Gly Val Arg Pro Lys Ala Leu Pro Val
145                 150                 155                 160

Gly Gly Lys Asp Leu Lys Glu Ile Asn Asp Trp Val Ser Gln Glu Thr
                165                 170                 175

Gly Gly Lys Val Gln Arg Phe Leu Ala Lys Pro Ser Ser Arg Asn Pro
            180                 185                 190

Ser Val Asn Thr Val Ser Ala Ala Tyr Phe Lys Gly Arg Trp Val Thr
        195                 200                 205

Arg Phe Ser Asn Ser Gly Val Met Glu Glu Phe Gln Val Asp Gly Ala
    210                 215                 220

Ala Pro Val Arg Val Pro Met Met Gln Gln Asp Asn Tyr Pro Val Lys
225                 230                 235                 240

Met Gly Ala Asp Ser Asp Leu Ser Cys Thr Ile Ala Gln Ile Gln Met
                245                 250                 255

Gln Asn Asp Val Ser Met Phe Ile Phe Leu Pro Asp Glu Val Met Ser
            260                 265                 270

Asn Met Thr Leu Leu Glu Glu Ser Leu Thr Ala Glu Phe Val Gln Asp
        275                 280                 285

Leu Ser Met Thr Leu Leu Pro Ala Gln Val Ser Leu Thr Leu Pro Thr
    290                 295                 300

Leu Arg Leu Ser Tyr Ser Thr Asp Leu Leu Pro Leu Leu Ser Asp Leu
305                 310                 315                 320

Gly Leu Thr Asp Trp Met Glu Asn Pro Gln Leu Glu Lys Ile Ser Thr
                325                 330                 335

Gln Ala Ala Lys Leu Thr Ser Val Asn His Lys Val Ile Met Glu Thr
```

```
                340                 345                 350

Ala Pro Glu Gly Asp Gln Tyr Pro Gly Ala Met Ser Thr Pro Asn His
        355                 360                 365

Leu Ser Tyr Arg Val Asp Arg Pro Phe Leu Tyr Leu Ile Arg Asp Glu
    370                 375                 380

Ala Ser Gly Ala Leu Leu Phe Ile Gly Arg Val Val Asn Pro Lys Asp
385                 390                 395                 400

Leu Arg Ile
```

Claims

1. An agonist of the OA1 receptor for use in treating or preventing age-related macular degeneration (AMD), wherein the agonist of the OA1 receptor is L-DOPA.

Patentansprüche

1. Agonist des OA1-Rezeptors zum Gebrauch beim Behandeln oder Verhindern von altersbedingter Makuladegeneration (AMD), wobei der Agonist des OA1-Rezeptors L-DOPA ist.

Revendications

1. Agoniste du récepteur OA1 pour une utilisation dans le traitement ou la prévention de la dégénérescence maculaire liée à l'âge (DMLA), où l'agoniste du récepteur OA1 est L-DOPA.

Figure 1

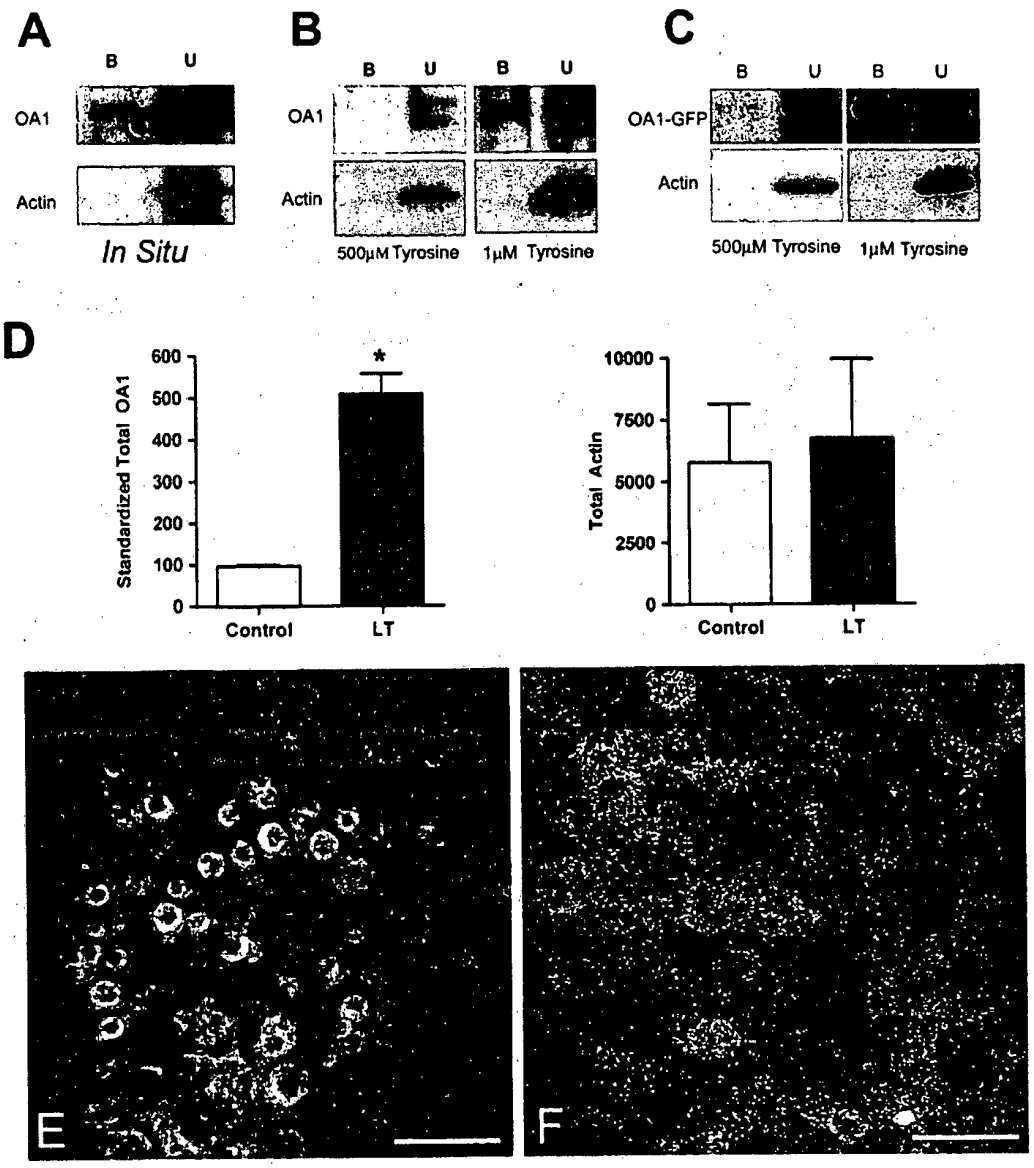
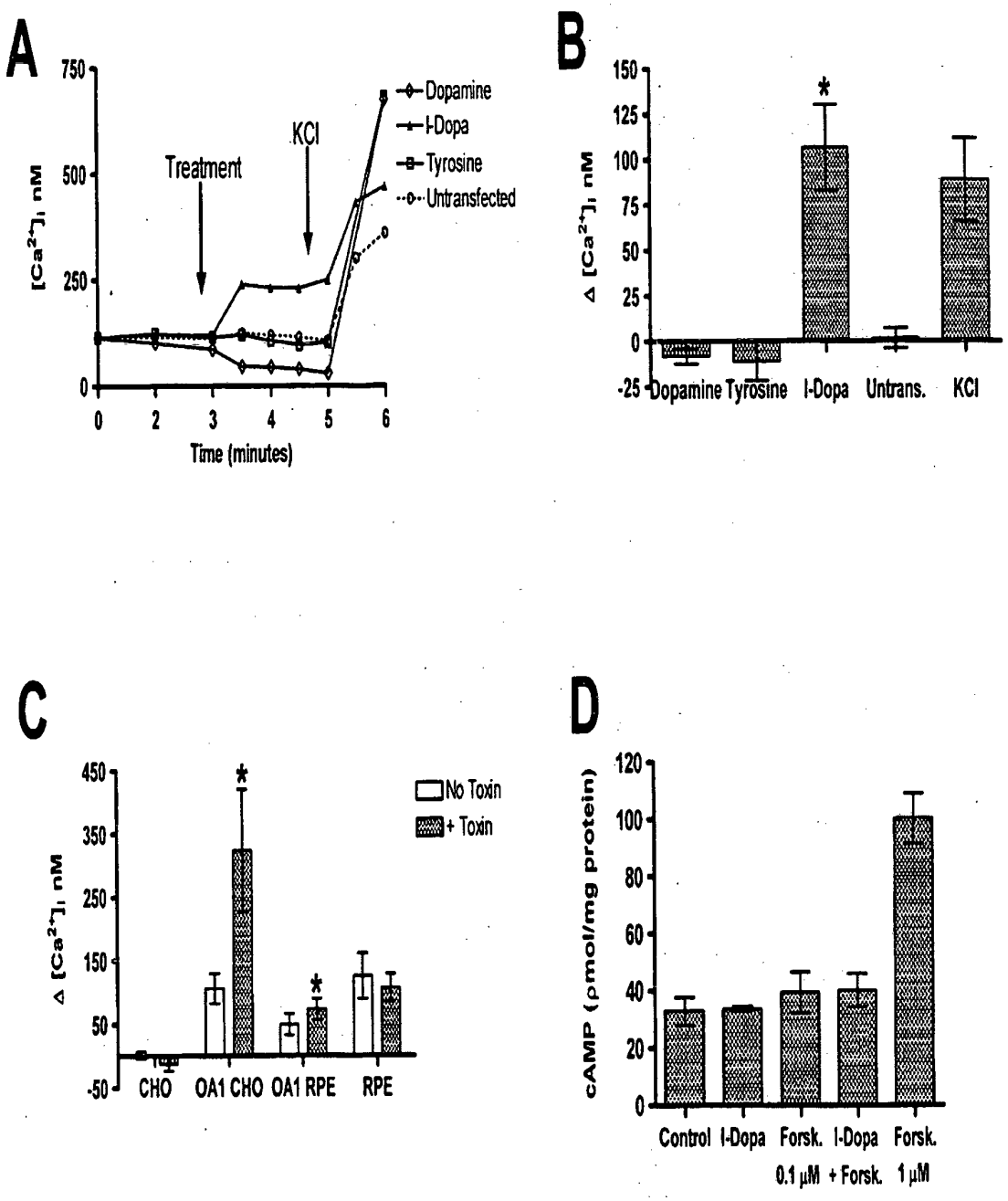

A
B
U
OA1
Actin
In Situ
B
U
B
U
OA1
Actin
500µM Tyrosine
1µM Tyrosine
C
B
U
B
U
OA1-GFP
Actin
500µM Tyrosine
1µM Tyrosine
D
Standardized Total OA1
600
500
400
300
200
100
0
*
Control
LT
Total Actin
10000
7500
5000
2500
0
Control
LT
E
F

Figure 2


A
750
500
250
0
[Ca2+]i nM
Treatment
KCl
Dopamine
l-Dopa
Tyrosine
Untransfected
0 2 3 4 5 6
Time (minutes)
B
150
125
100
75
50
25
0
-25
Δ [Ca2+]i nM
*
Dopamine Tyrosine l-Dopa Untrans. KCl
C
450
350
250
150
50
-50
Δ [Ca2+]i nM
*
*
No Toxin
+ Toxin
CHO OA1 CHO OA1 RPE RPE
D
120
100
80
60
40
20
0
cAMP (pmol/mg protein)
Control l-Dopa Forsk. l-Dopa Forsk.
0.1 µM + Forsk. 1 µM

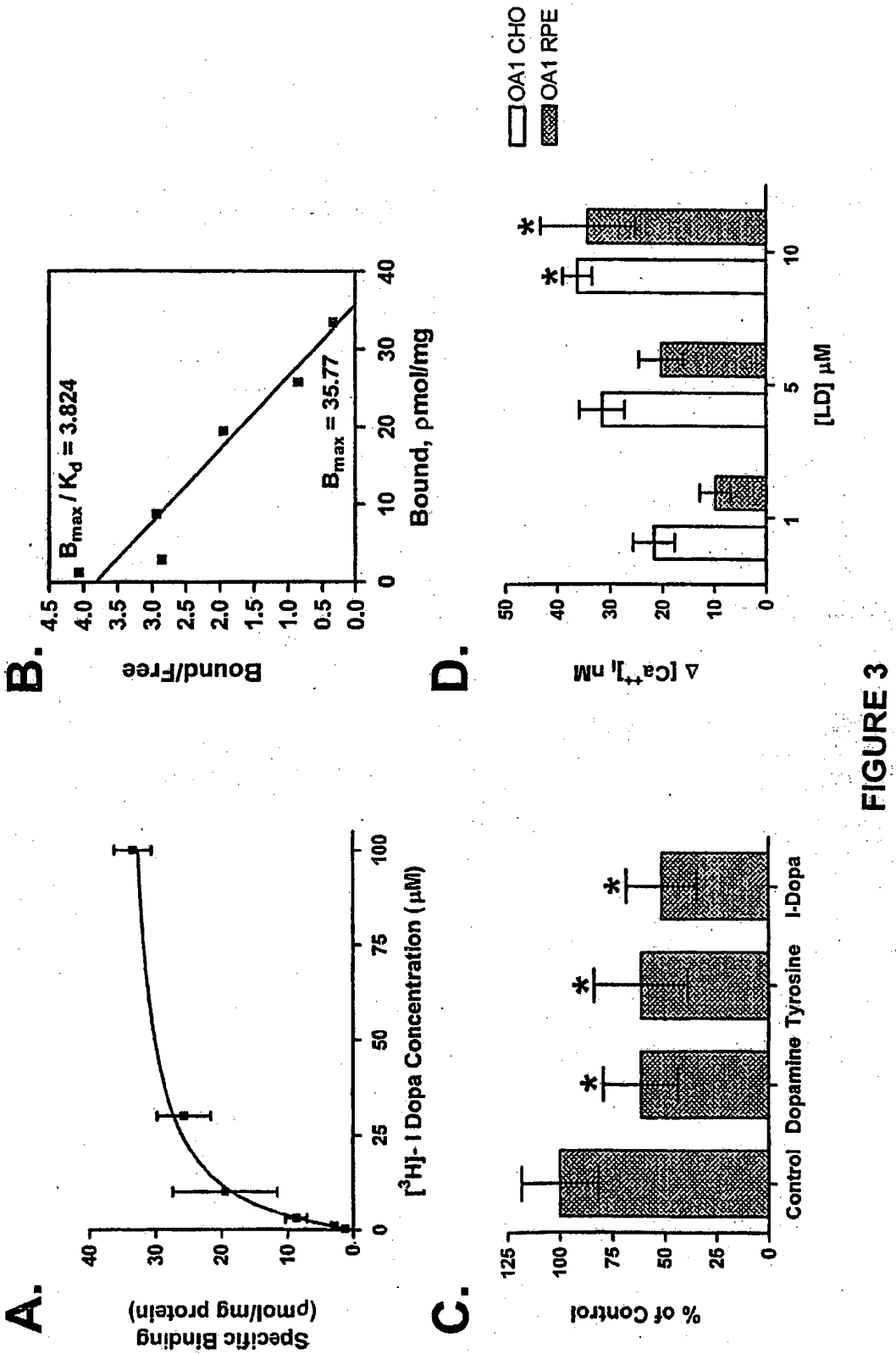

A.
Specific Binding (pmol/mg protein)
[3H]- l Dopa Concentration (μM)
B.
Bound/Free
Bound, pmol/mg
Bmax / Kd = 3.824
Bmax = 35.77
C.
% of Control
Control
Dopamine
Tyrosine
l-Dopa
D.
Δ [Ca++]i nM
[LD] μM
OA1 CHO
OA1 RPE

FIGURE 3

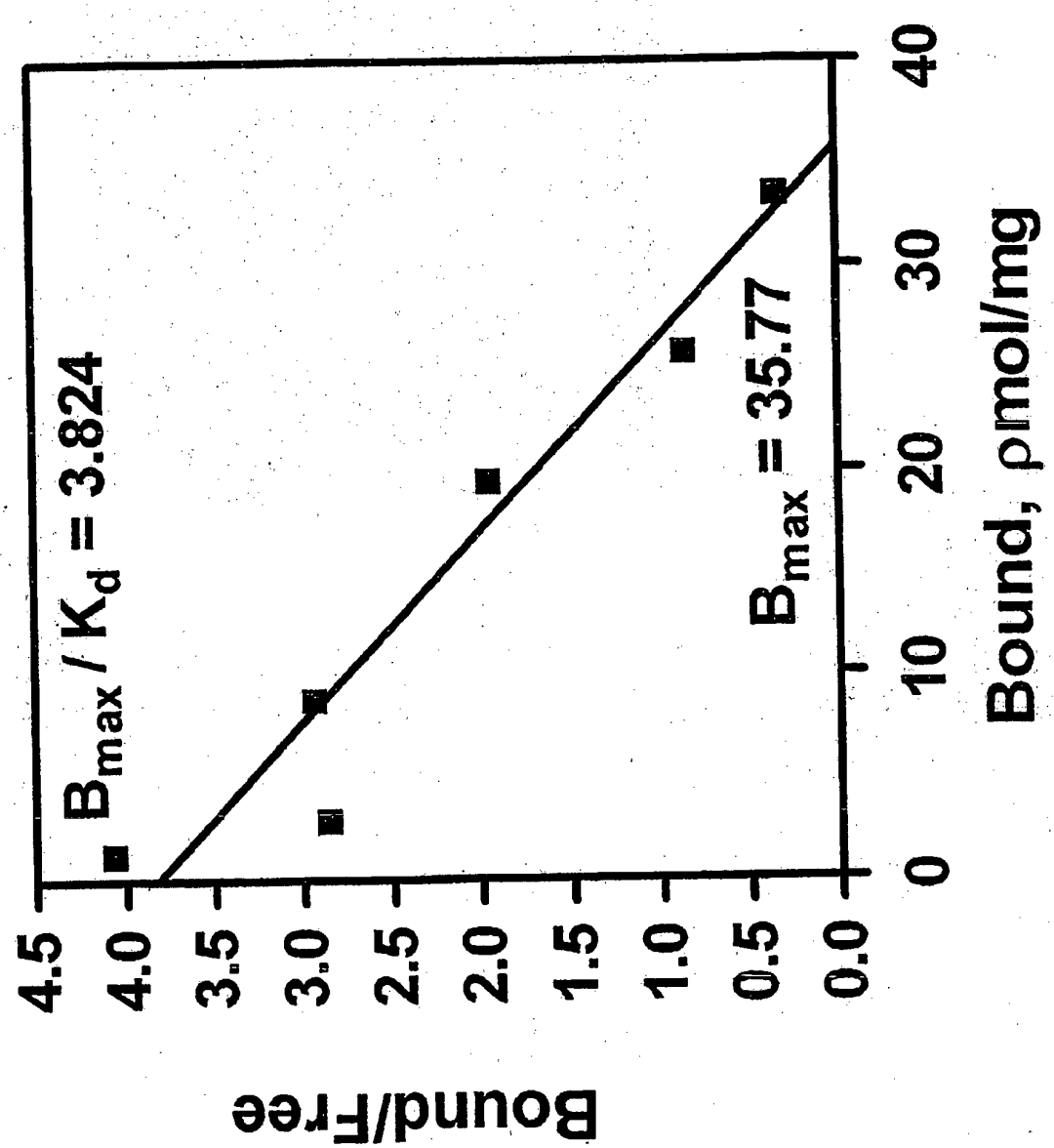

Bound/Free
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Bound, pmol/mg
B_{max} / K_d = 3.824
B_{max} = 35.77

FIGURE 3E

Figure 4

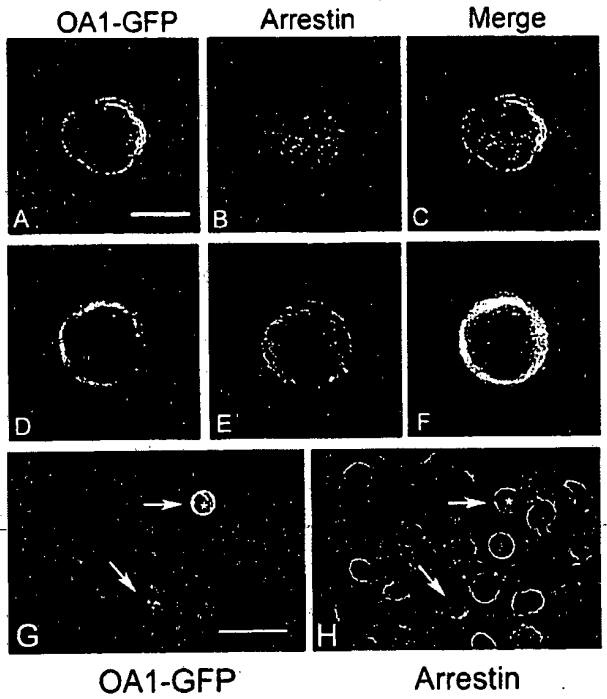


Figure 5

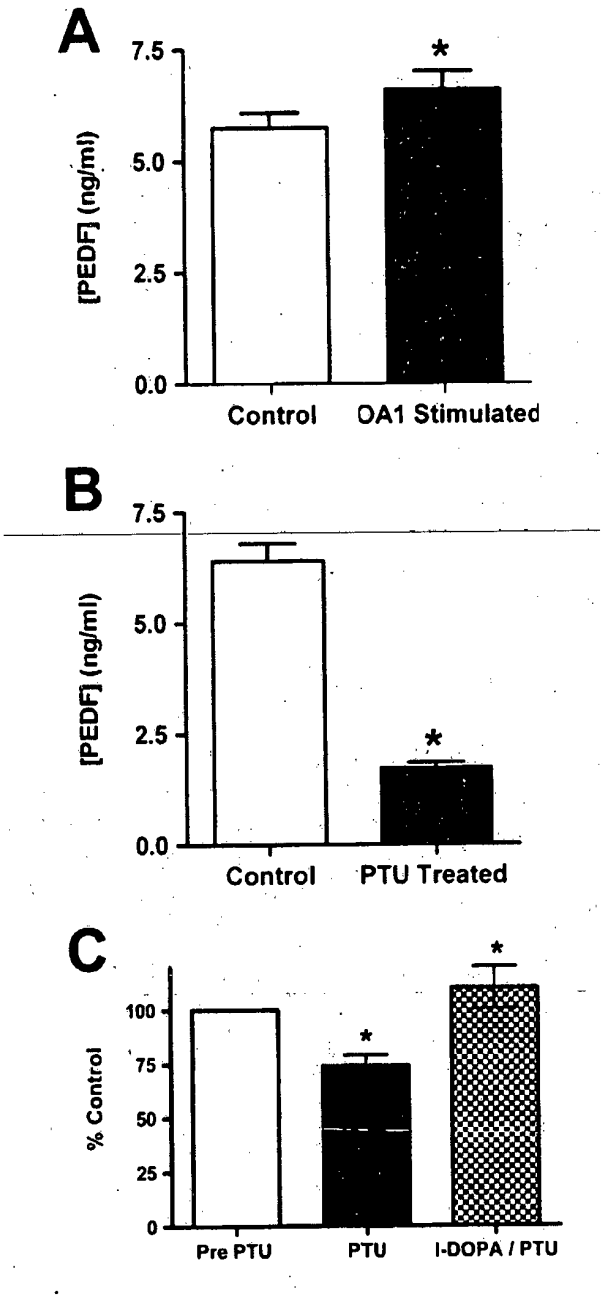

A
7.5
5.0
2.5
0.0
[PEDF] (ng/ml)
*
Control
OA1 Stimulated
B
7.5
5.0
2.5
0.0
[PEDF] (ng/ml)
*
Control
PTU Treated
C
100
75
50
25
0
% Control
*
*
Pre PTU
PTU
l-DOPA / PTU

Figure 6

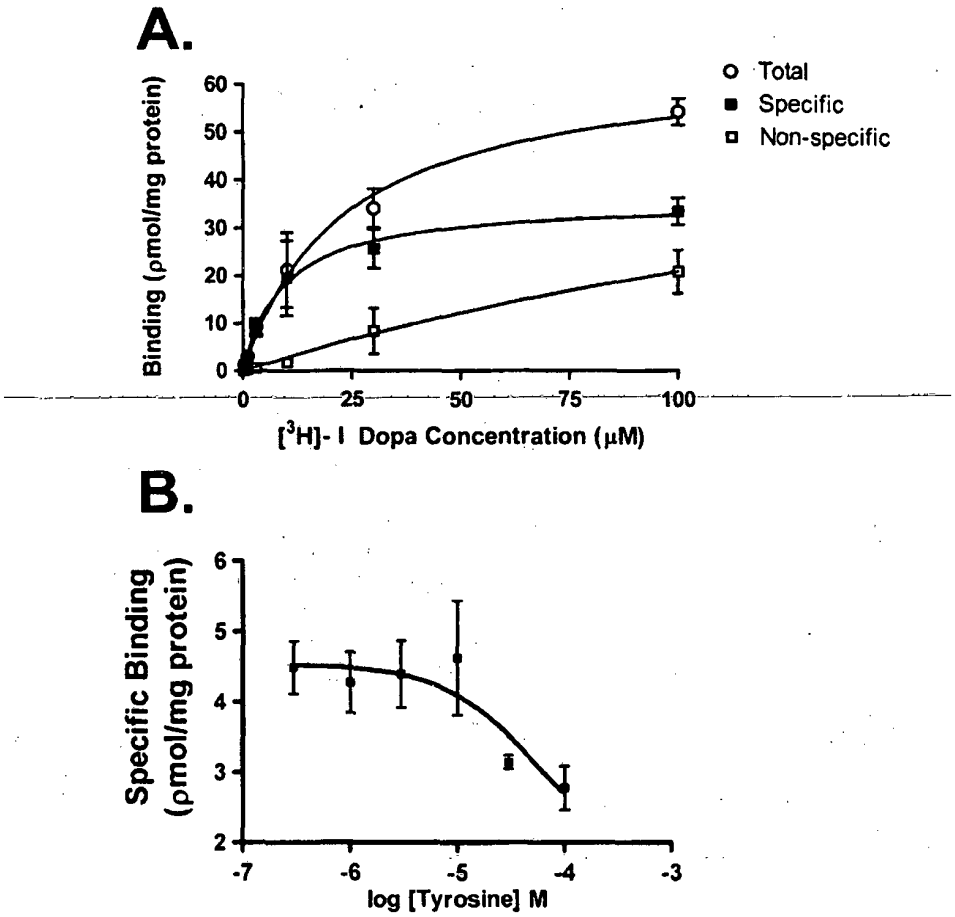

A.
Binding (pmol/mg protein)
60
50
40
30
20
10
0
0
25
50
75
100
[3H]- l Dopa Concentration (μM)
Total
Specific
Non-specific
B.
Specific Binding (pmol/mg protein)
6
5
4
3
2
-7
-6
-5
-4
-3
log [Tyrosine] M

Figure 7

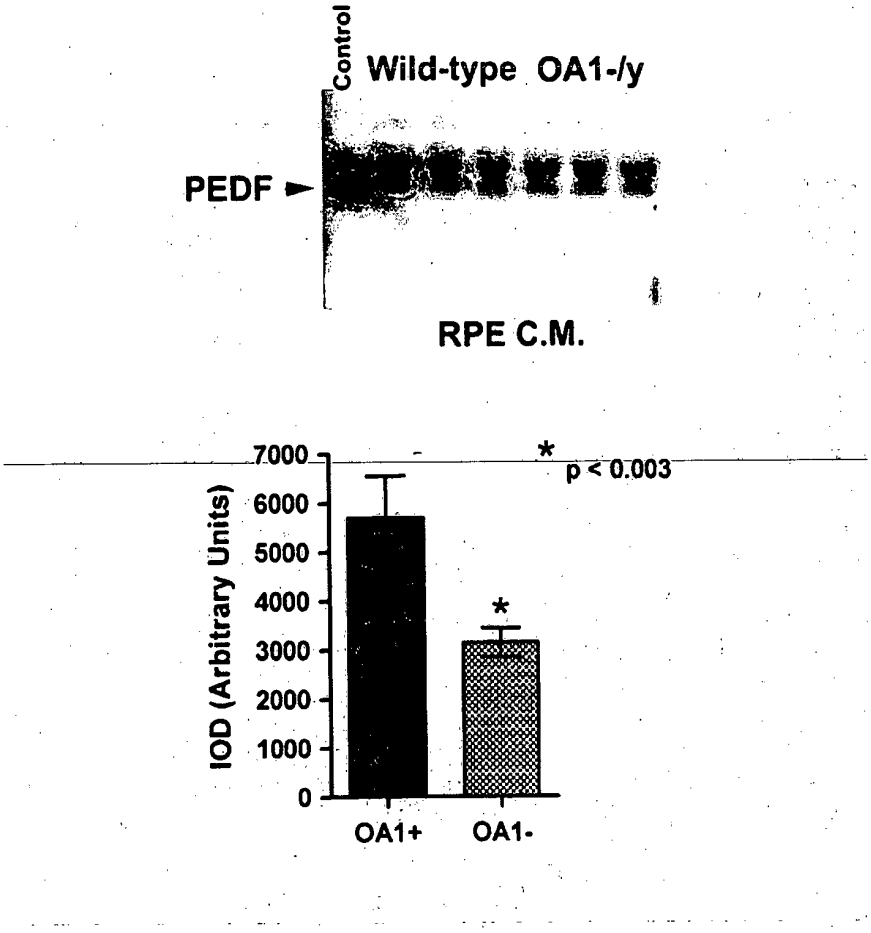
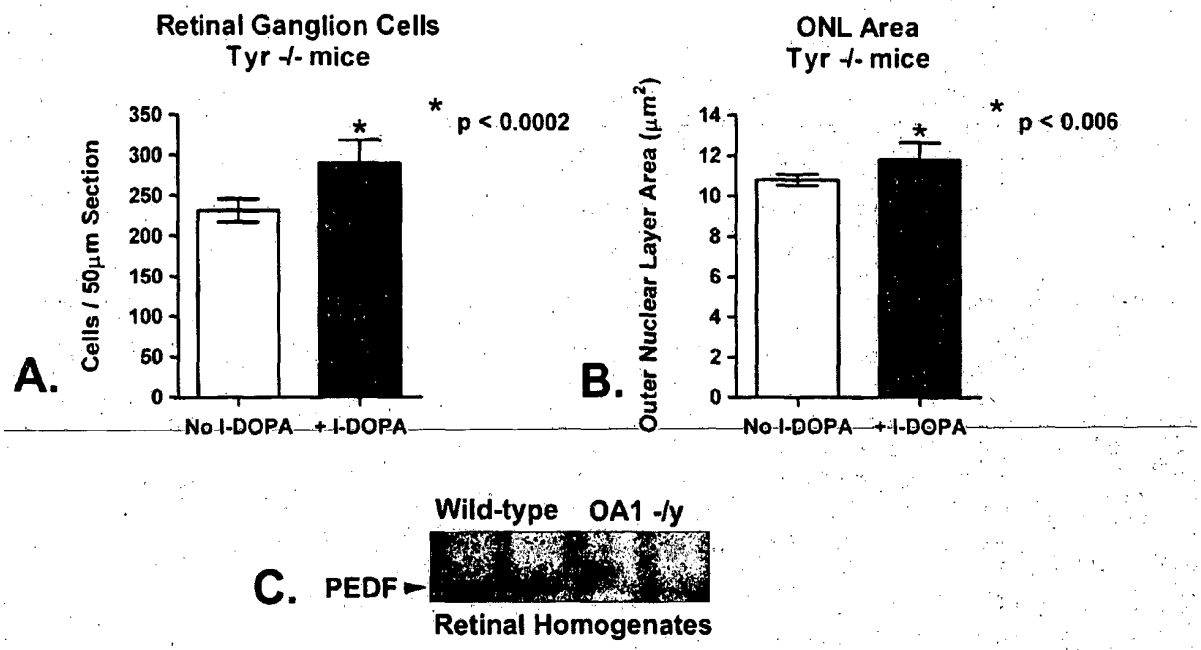

Control
Wild-type
OA1-/y
PEDF
RPE C.M.
IOD (Arbitrary Units)
7000
6000
5000
4000
3000
2000
1000
0
*
p < 0.003
*
OA1+
OA1-

Figure 8


Retinal Ganglion Cells
Tyr -/- mice
A.
Cells / 50µm Section
350
300
250
200
150
100
50
0
*
p < 0.0002
No l-DOPA
+ l-DOPA
ONL Area
Tyr -/- mice
B.
Outer Nuclear Layer Area (µm²)
14
12
10
8
6
4
2
0
*
p < 0.006
No l-DOPA
+ l-DOPA
Wild-type
OA1 -/y
C.
PEDF
Retinal Homogenates

REFERENCES CITED IN THE DESCRIPTION

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