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(12) **United States Patent**
Gao et al.(10) **Patent No.:** US 12,390,539 B2
(45) **Date of Patent:** Aug. 19, 2025(54) **MINIGENE THERAPY**(71) Applicant: **University of Massachusetts**,
Westborough, MA (US)(72) Inventors: **Guangping Gao**, Worcester, MA (US);
Hemant Khanna, Worcester, MA (US)(73) Assignee: **University of Massachusetts**,
Westborough, MA (US)

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(21) Appl. No.: **17/612,653**(22) PCT Filed: **May 19, 2020**(86) PCT No.: **PCT/US2020/033600**

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(2) Date: **Nov. 19, 2021**(87) PCT Pub. No.: **WO2020/236815**PCT Pub. Date: **Nov. 26, 2020**(65) **Prior Publication Data**

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Related U.S. Application Data(60) Provisional application No. 62/967,521, filed on Jan. 29, 2020, provisional application No. 62/899,601,
(Continued)(51) **Int. Cl.**
A61K 48/00 (2006.01)
A61K 35/76 (2015.01)
(Continued)(52) **U.S. Cl.**CPC *A61K 48/0058* (2013.01); *A61K 35/76* (2013.01); *A61P 27/02* (2018.01);
(Continued)(58) **Field of Classification Search**None
See application file for complete search history.(56) **References Cited**

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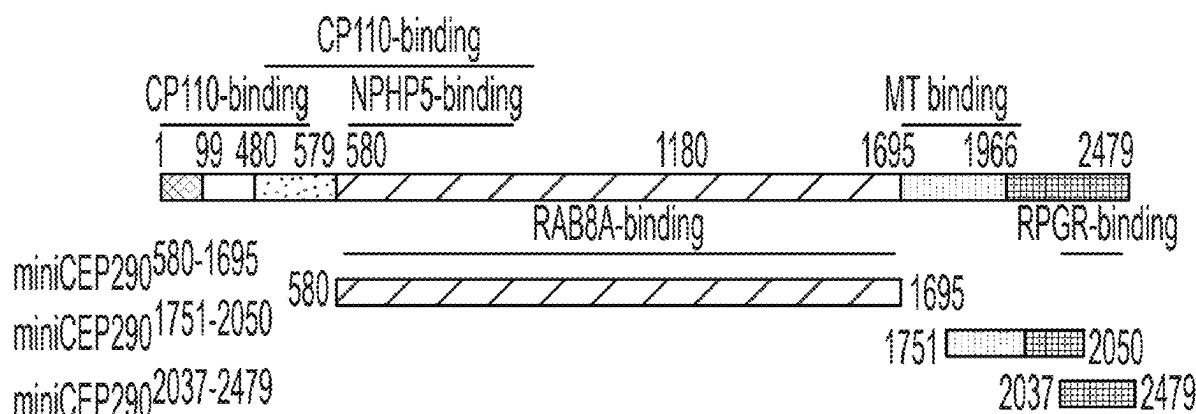
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(Continued)*Primary Examiner* — Marcia S Noble*Assistant Examiner* — Briana N Ebbinghaus(74) *Attorney, Agent, or Firm* — Wolf, Greenfield & Sacks, P.C.(57) **ABSTRACT**

Aspects of the disclosure relate to compositions and methods useful for treating ocular ciliopathies, for example Leber congenital amaurosis (LCA). In some embodiments, the disclosure provides isolated nucleic acids comprising a transgene encoding a CEP290 protein fragment, and methods of treating ocular ciliopathies using the same.

14 Claims, 34 Drawing Sheets**Specification includes a Sequence Listing.**

Related U.S. Application Data

filed on Sep. 12, 2019, provisional application No. 62/850,405, filed on May 20, 2019.

(51) **Int. Cl.**

A61P 27/02 (2006.01)
C07K 14/705 (2006.01)
CI2N 5/079 (2010.01)
CI2N 7/00 (2006.01)
CI2N 15/113 (2010.01)
CI2N 15/86 (2006.01)

(52) **U.S. Cl.**

CPC *C07K 14/705* (2013.01); *CI2N 5/0621* (2013.01); *CI2N 7/00* (2013.01); *CI2N 15/113* (2013.01); *CI2N 15/86* (2013.01); *CI2N 2310/10* (2013.01); *CI2N 2750/14122* (2013.01); *CI2N 2750/14142* (2013.01); *CI2N 2830/008* (2013.01)

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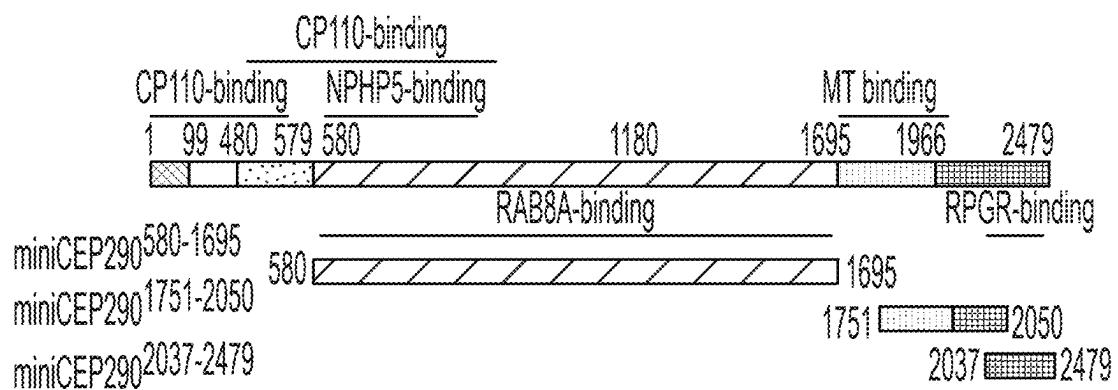


FIG. 1

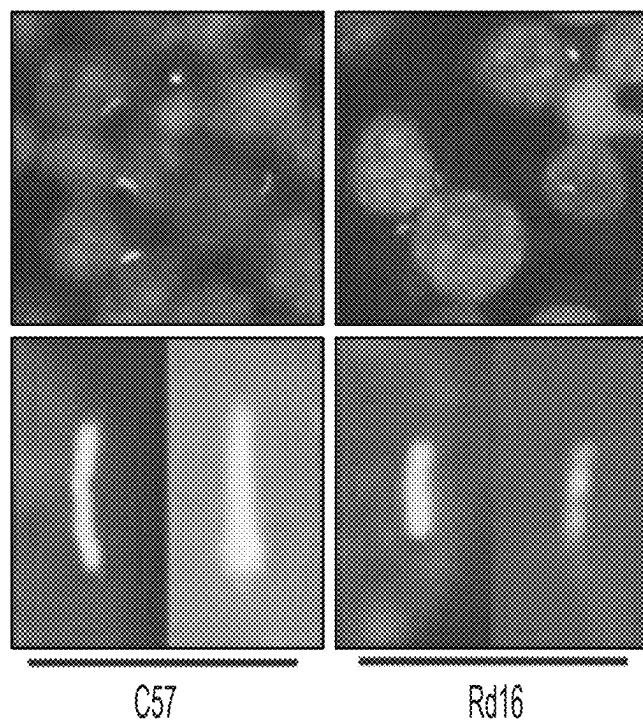


FIG. 2A

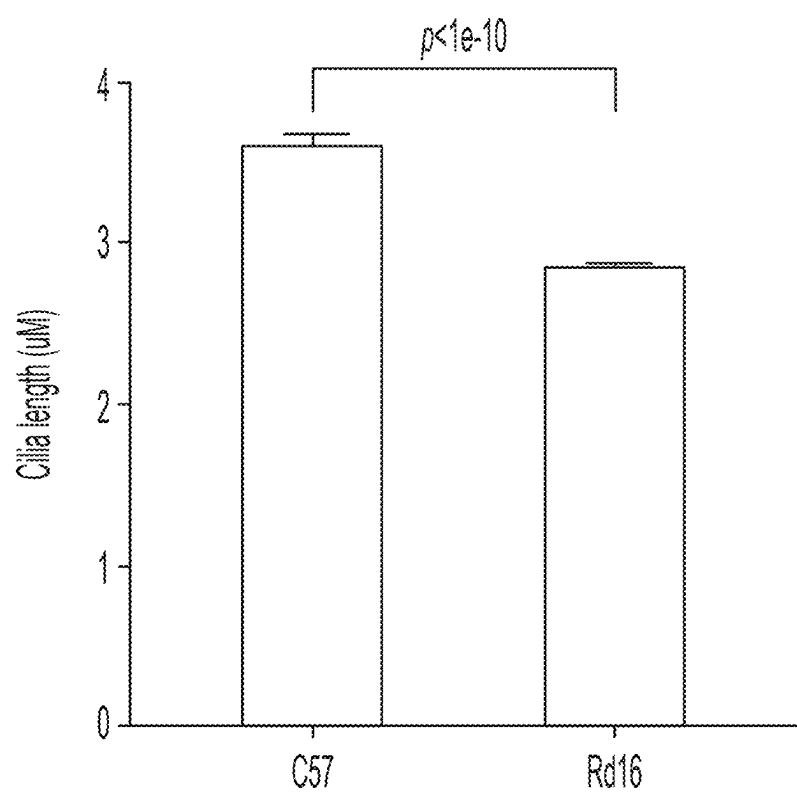
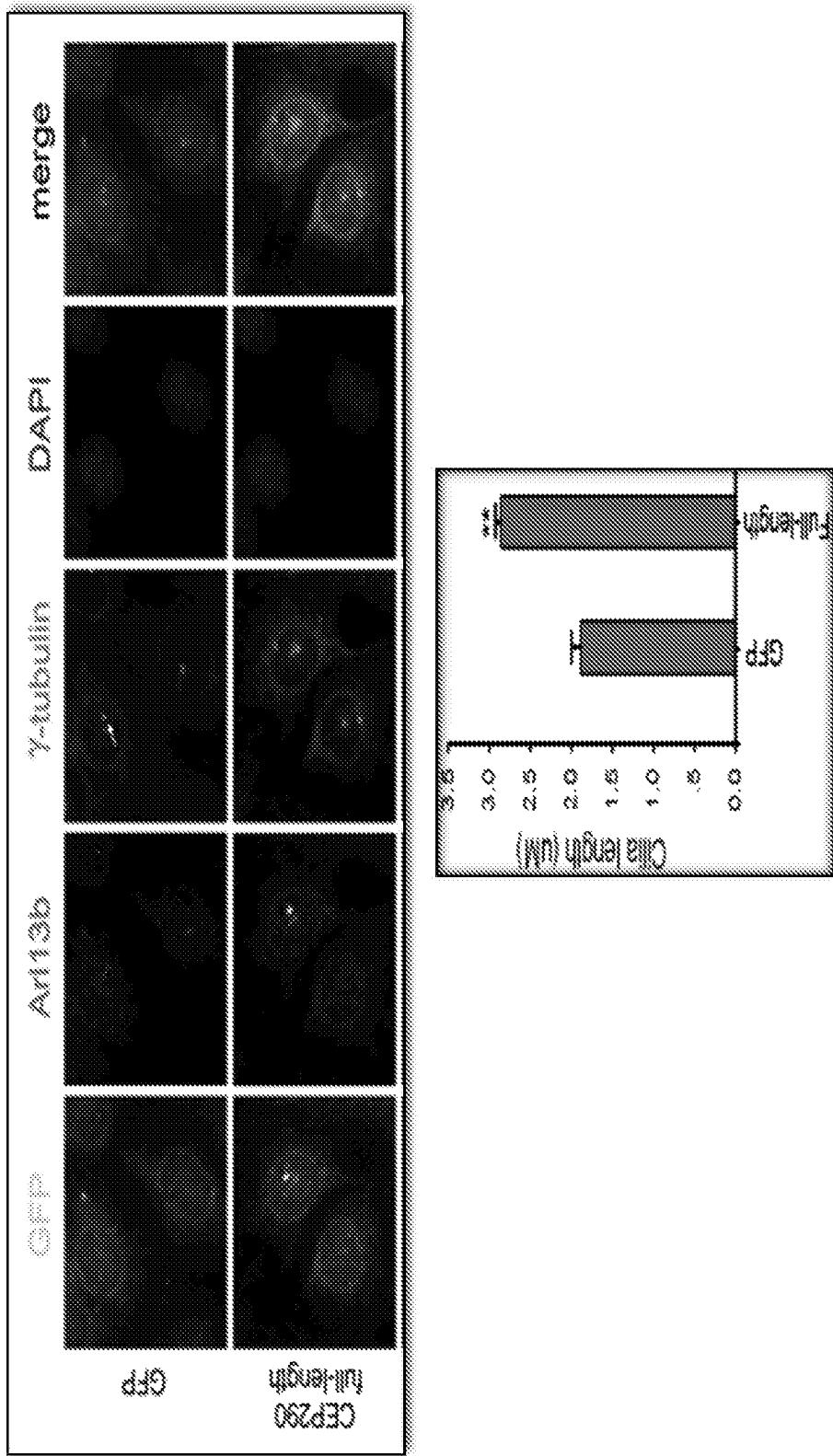


FIG. 2B

FIG. 3



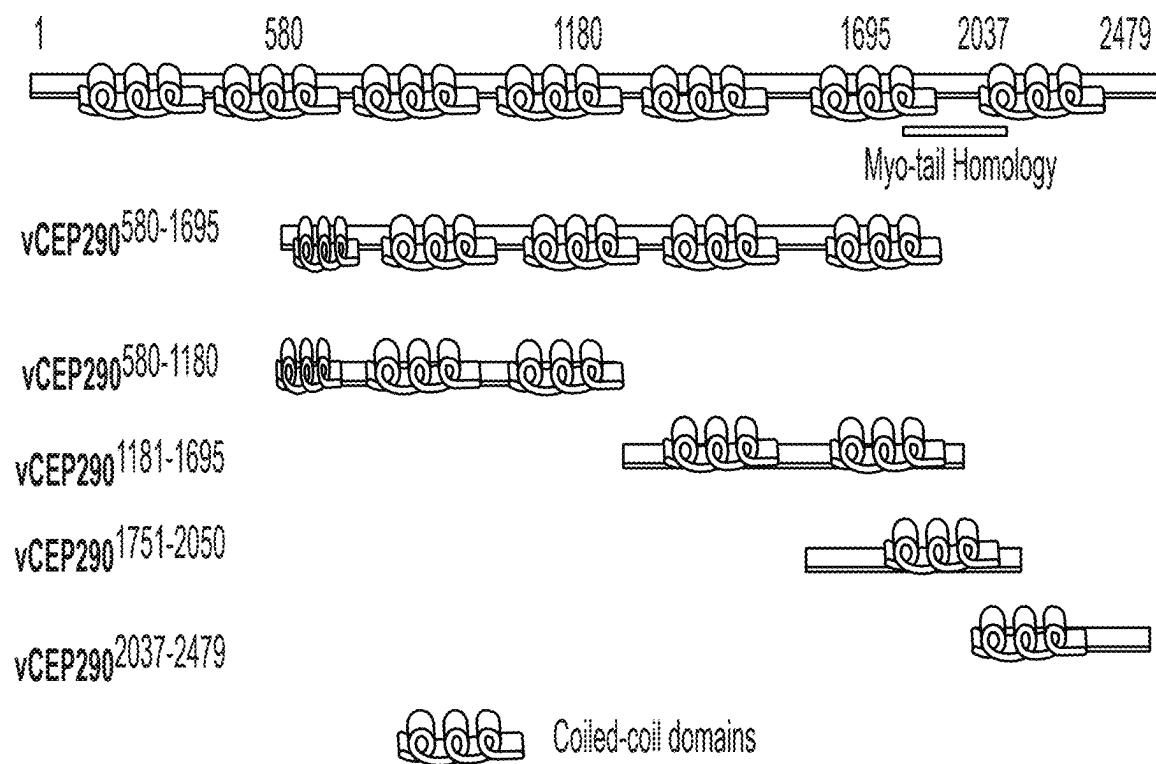


FIG. 4A

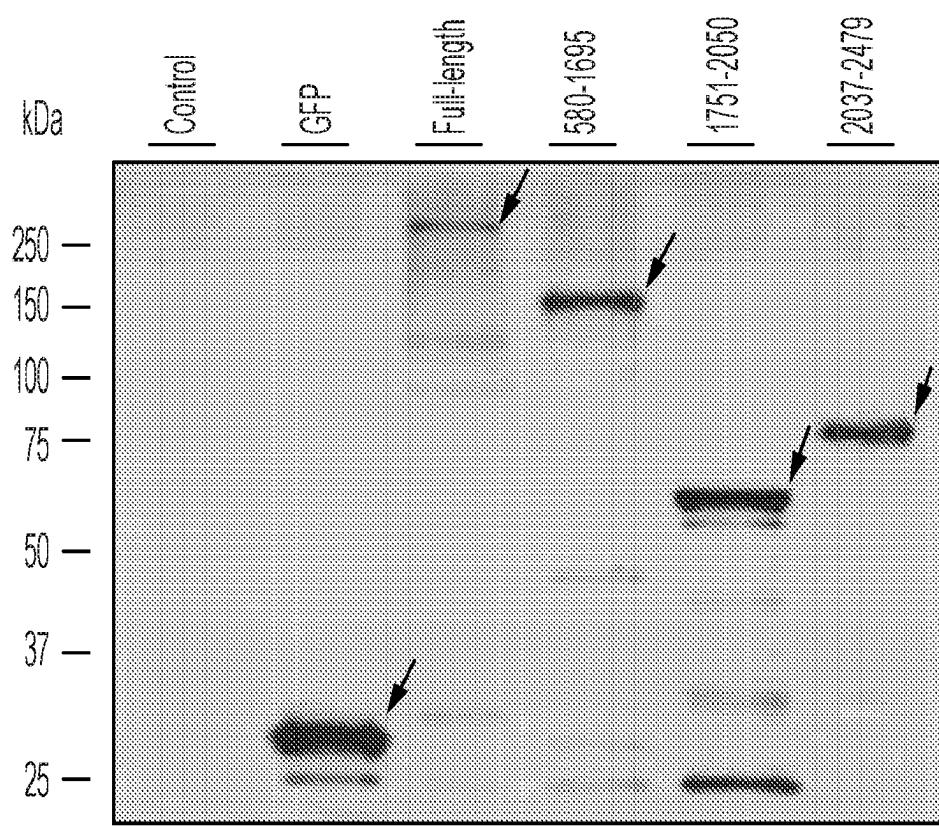


FIG. 4B

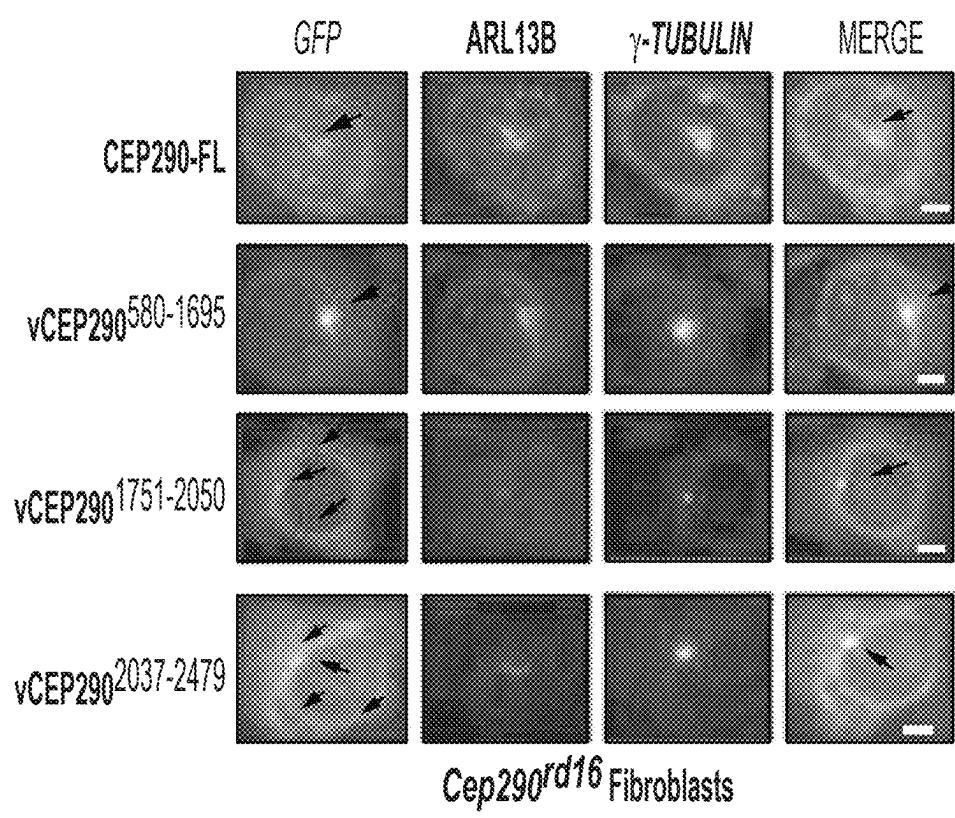
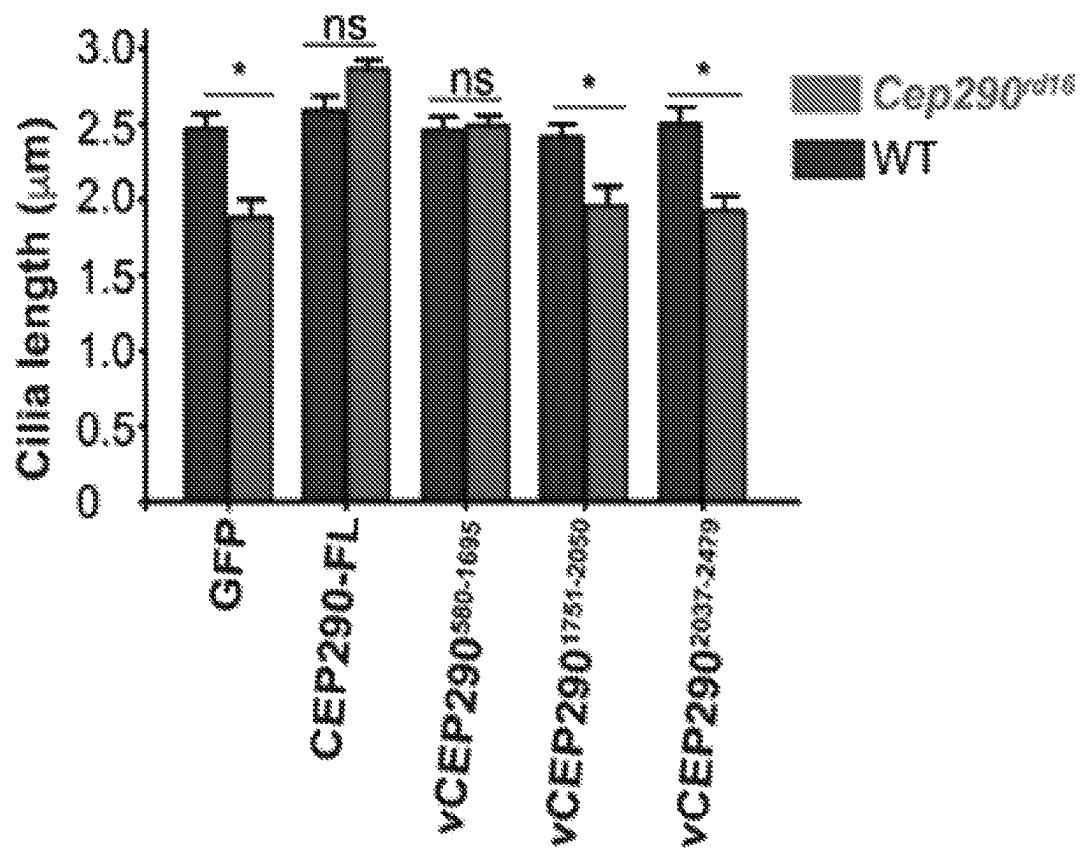


FIG. 5A

FIG. 5B

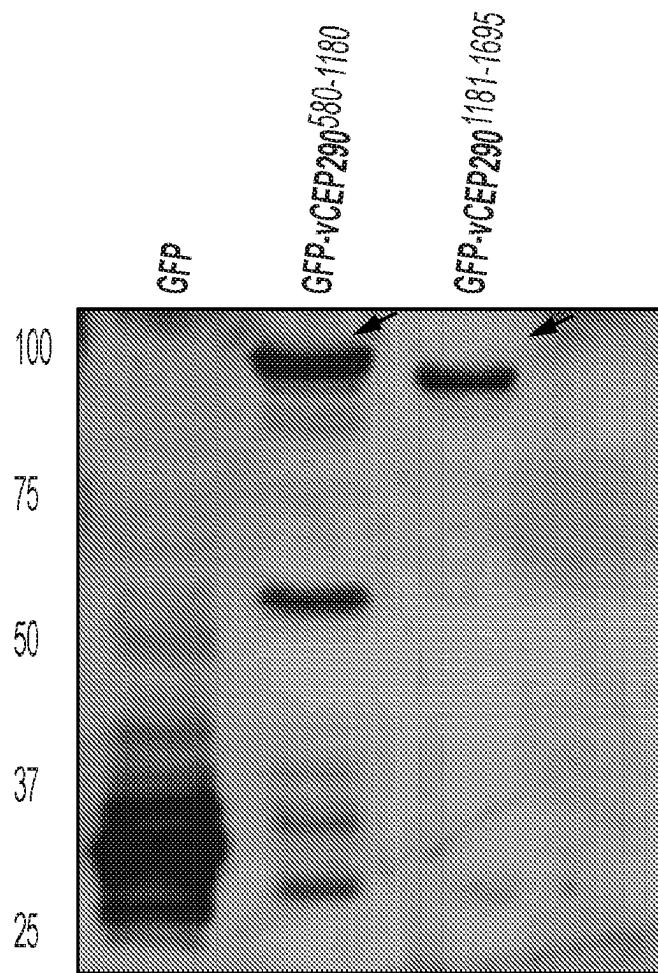


FIG. 6A

FIG. 6B

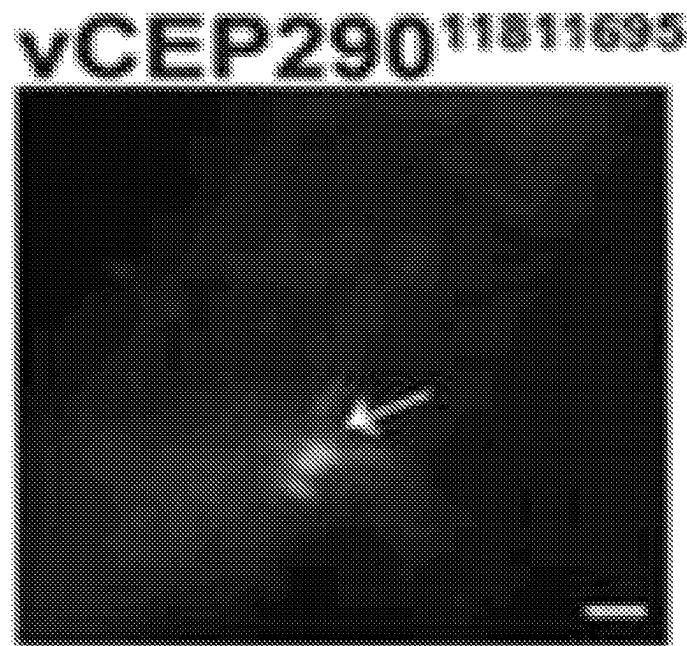
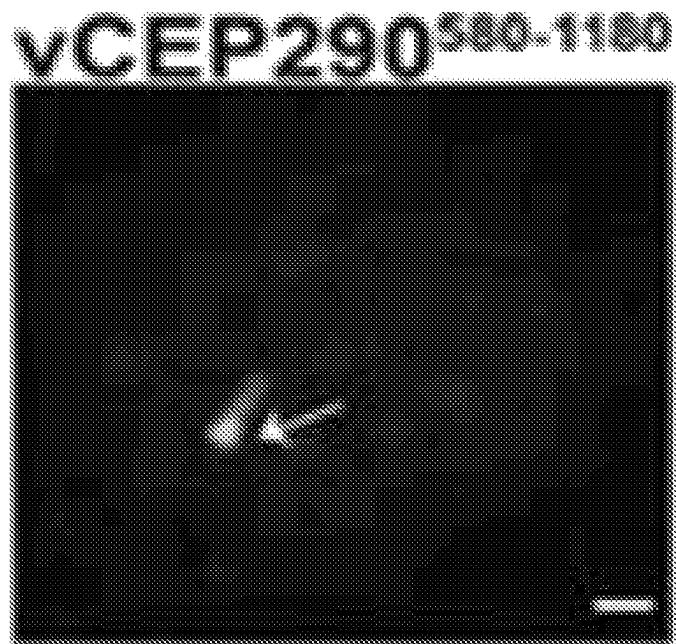
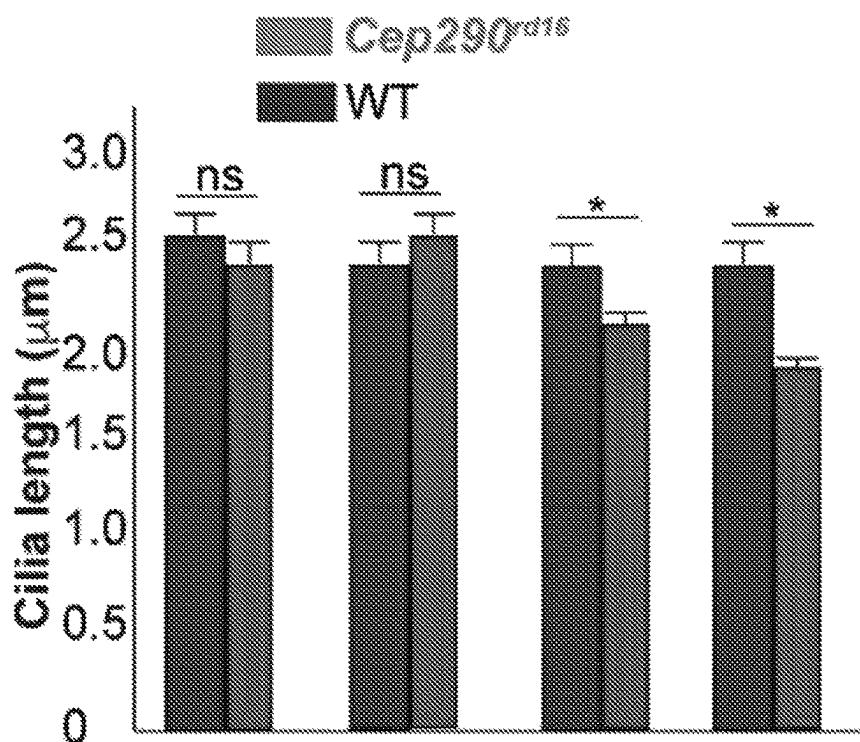


FIG. 6C



GFP	~	~	~	~
GFP-CEP290-FL	~	~	~	~
GFP- miniCEP290 ⁵⁸⁰⁻¹¹⁸⁰	~	~	~	~
GFP- miniCEP290 ¹¹⁸¹⁻¹⁶⁹⁵	~	~	~	~

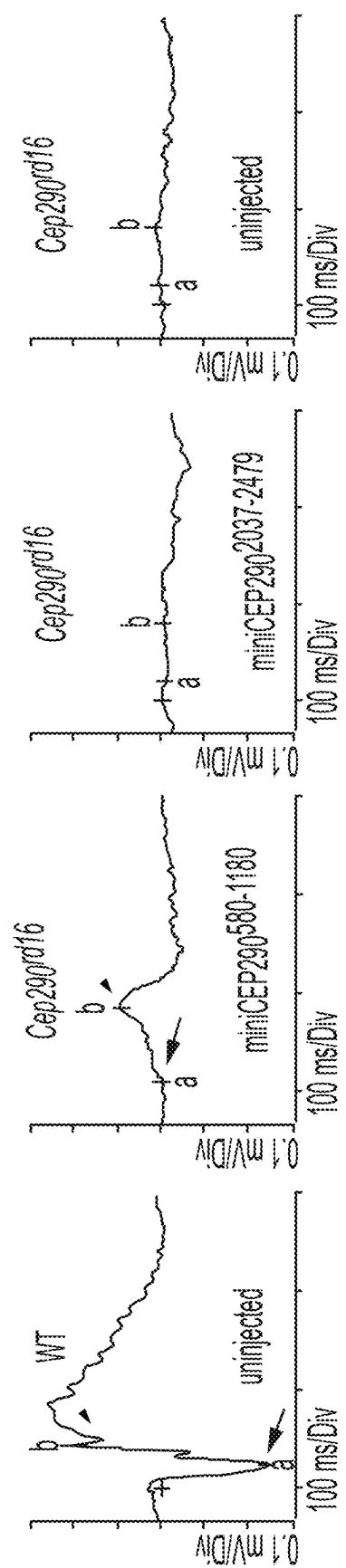


FIG. 7A

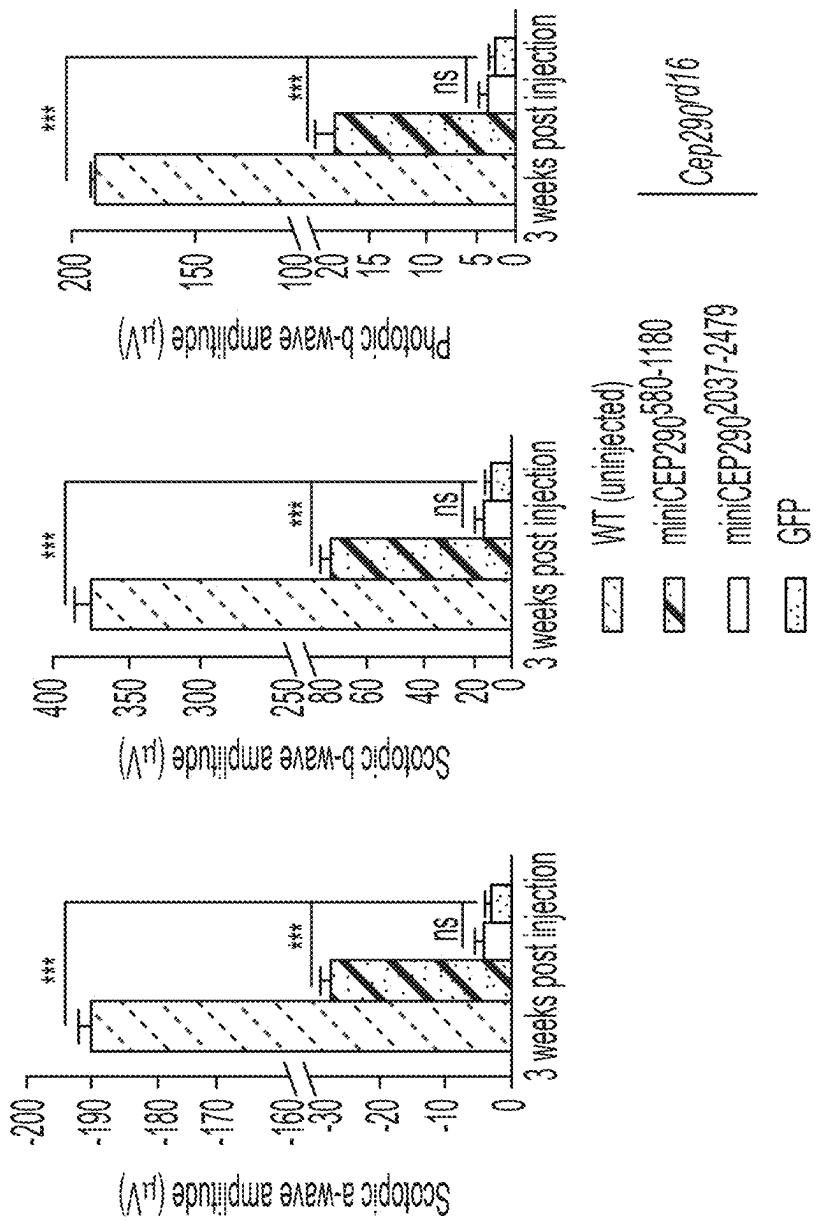
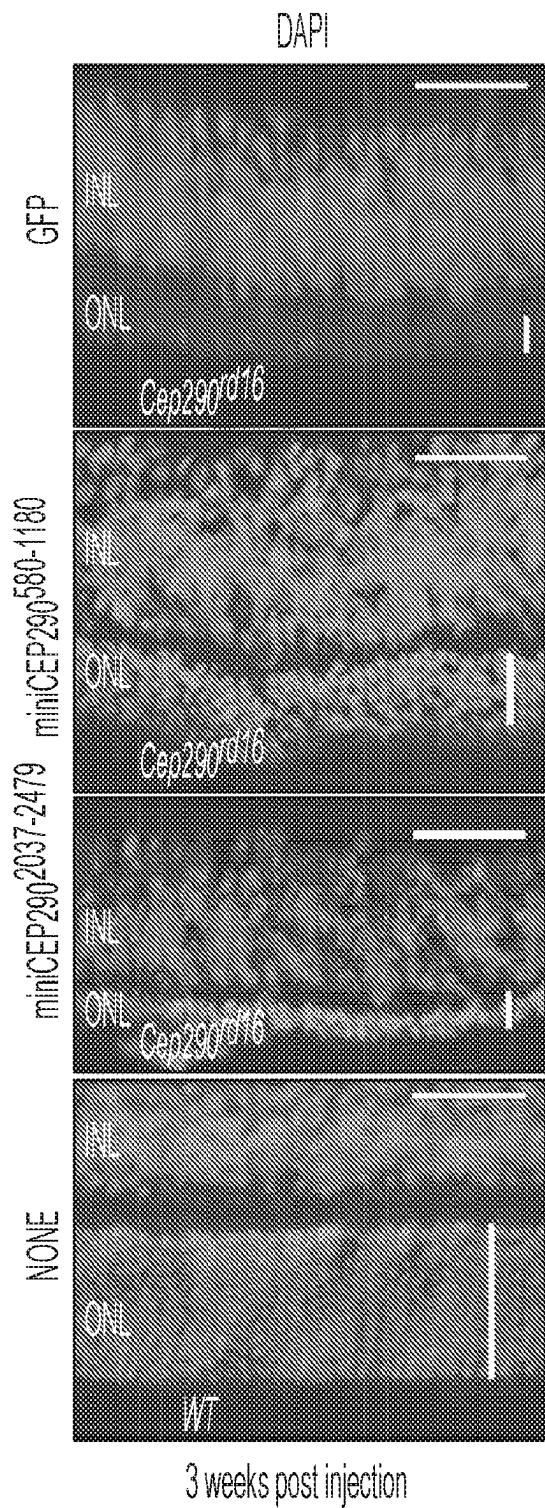


FIG. 7B



3 weeks post injection

FIG. 8A

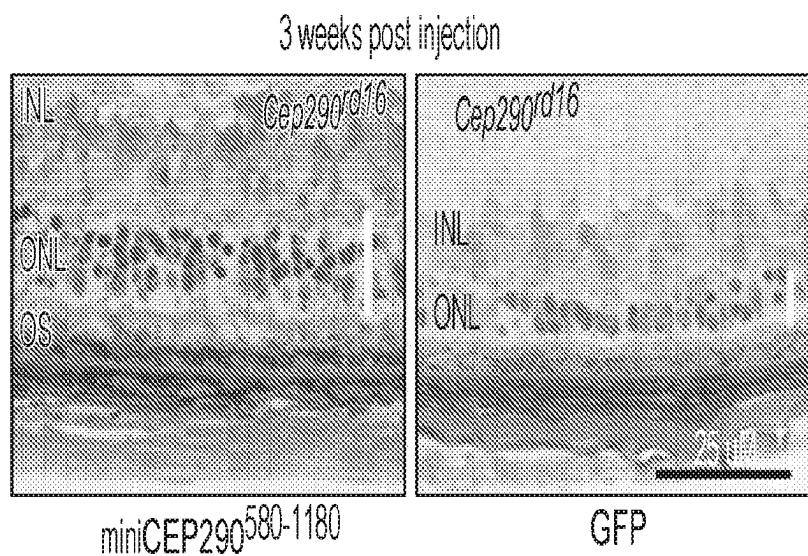


FIG. 8B

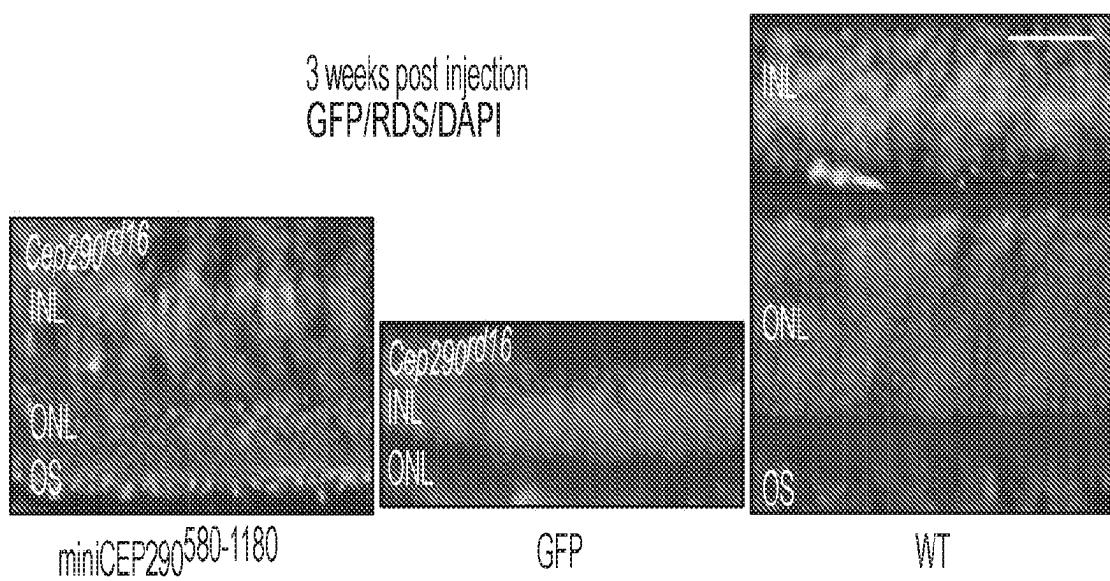


FIG. 8C

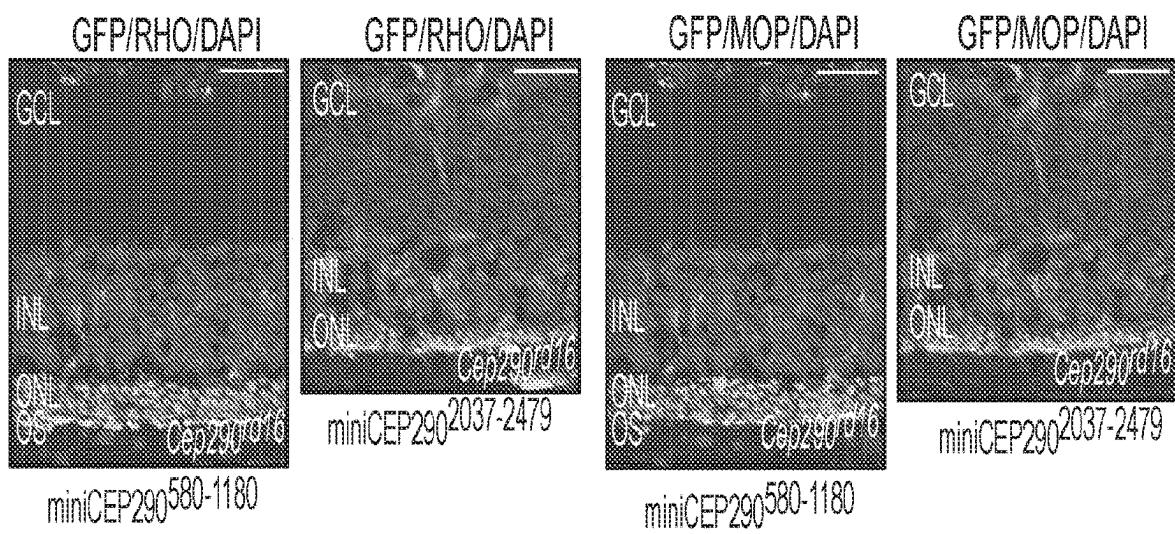


FIG. 8D

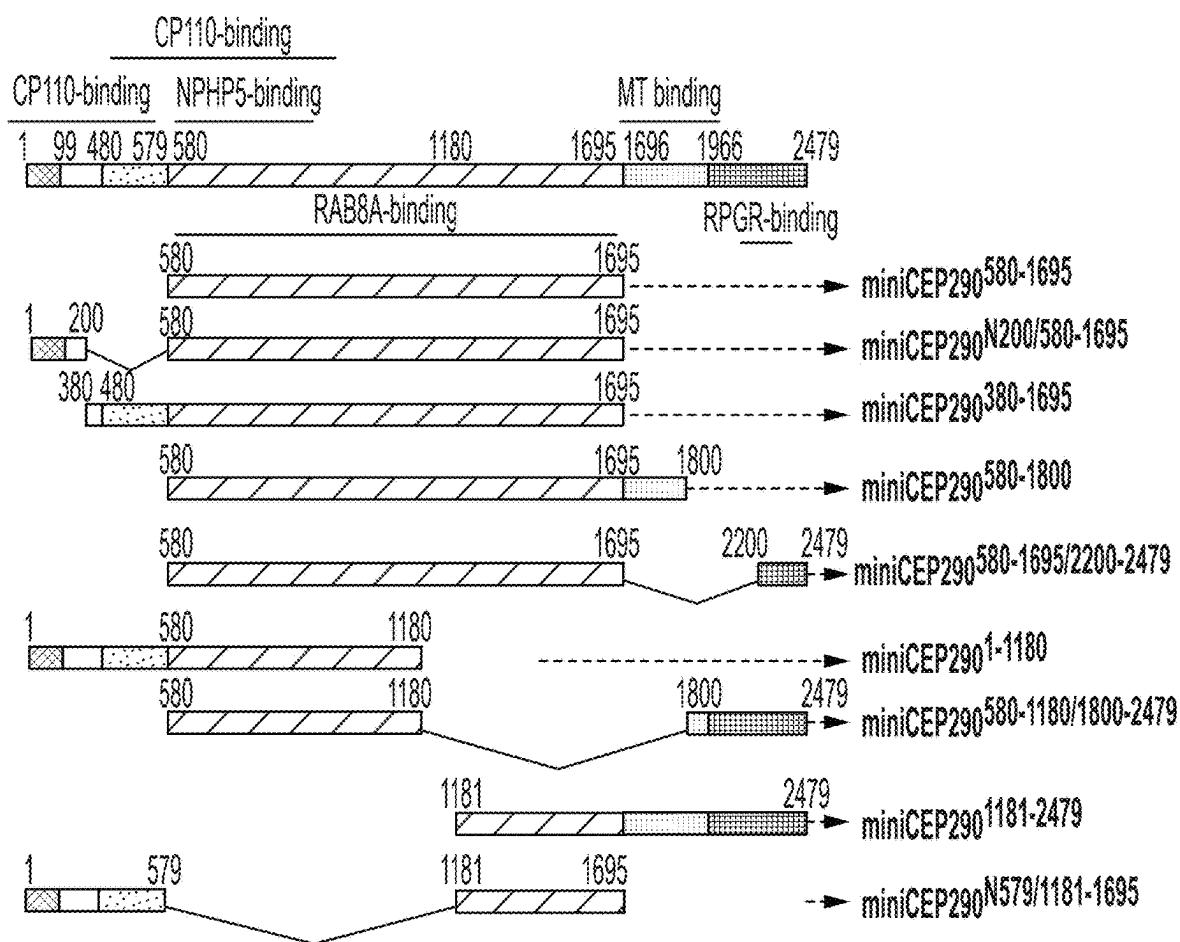
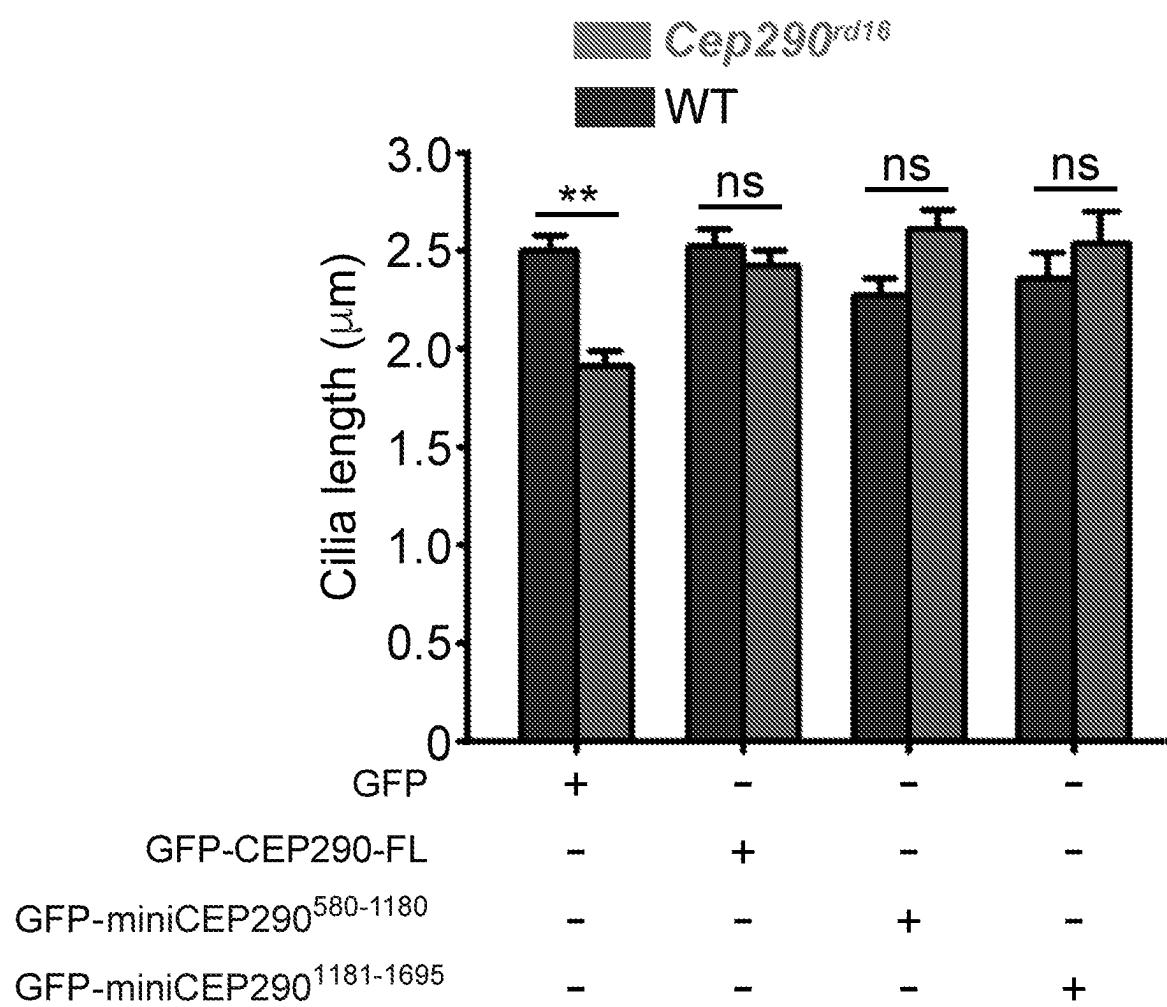


FIG. 9

FIG. 10

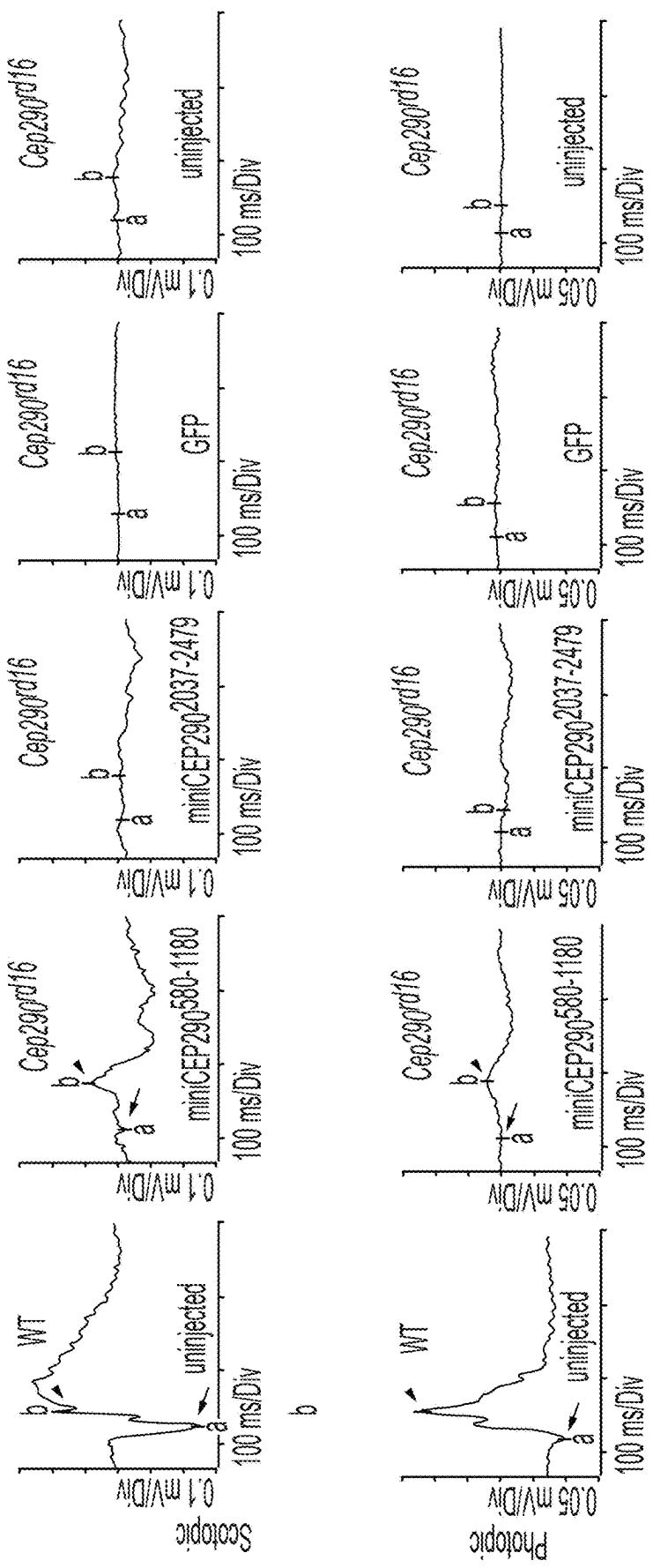
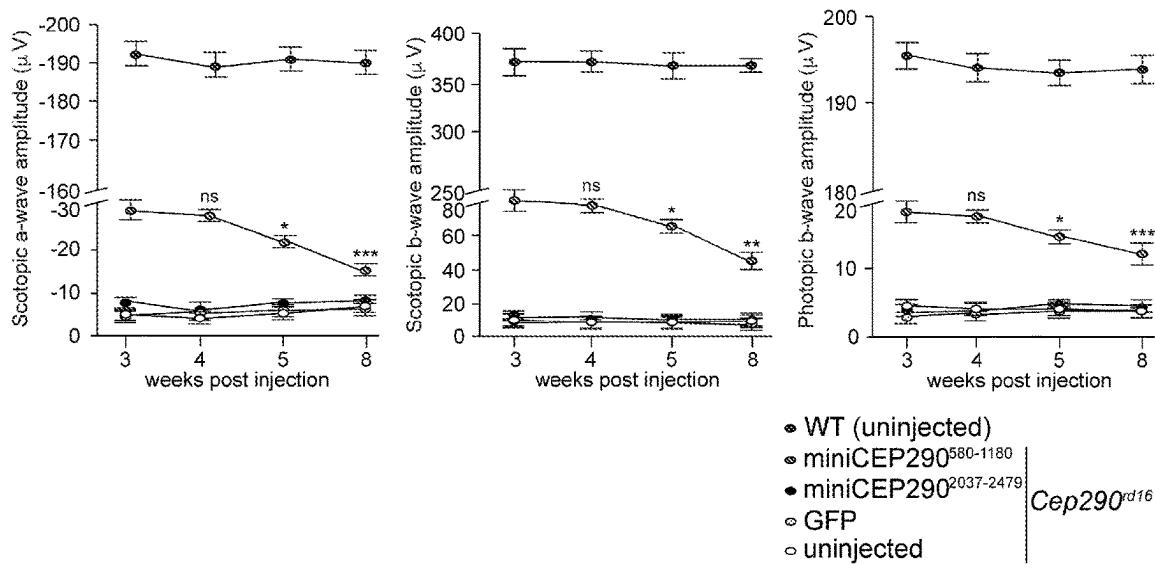
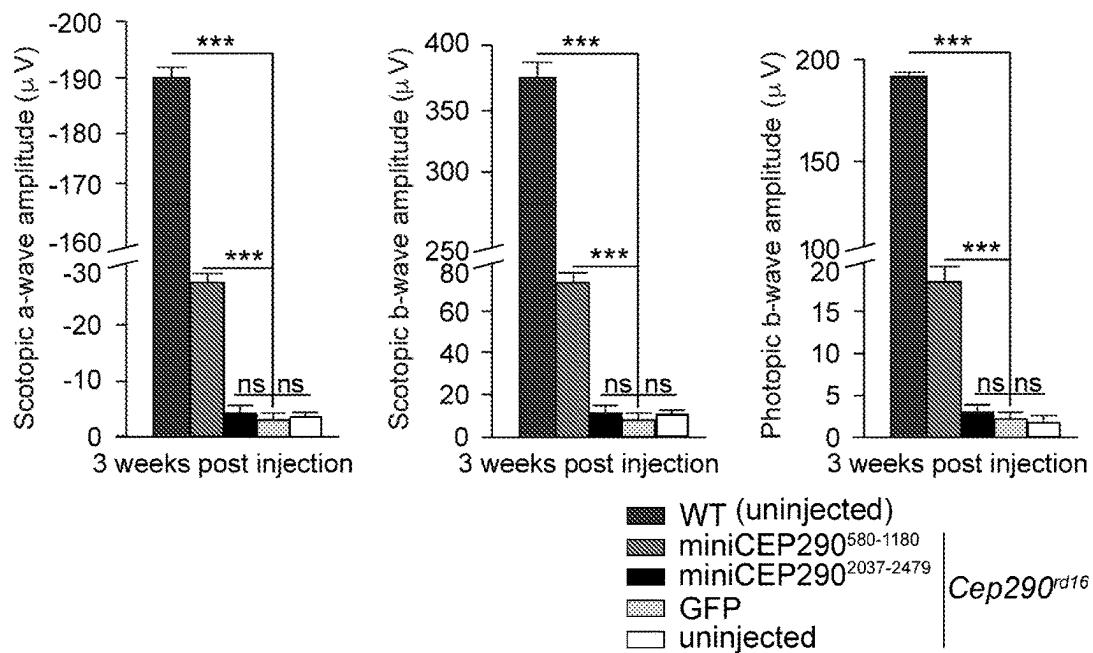


FIG. 11

FIG. 12

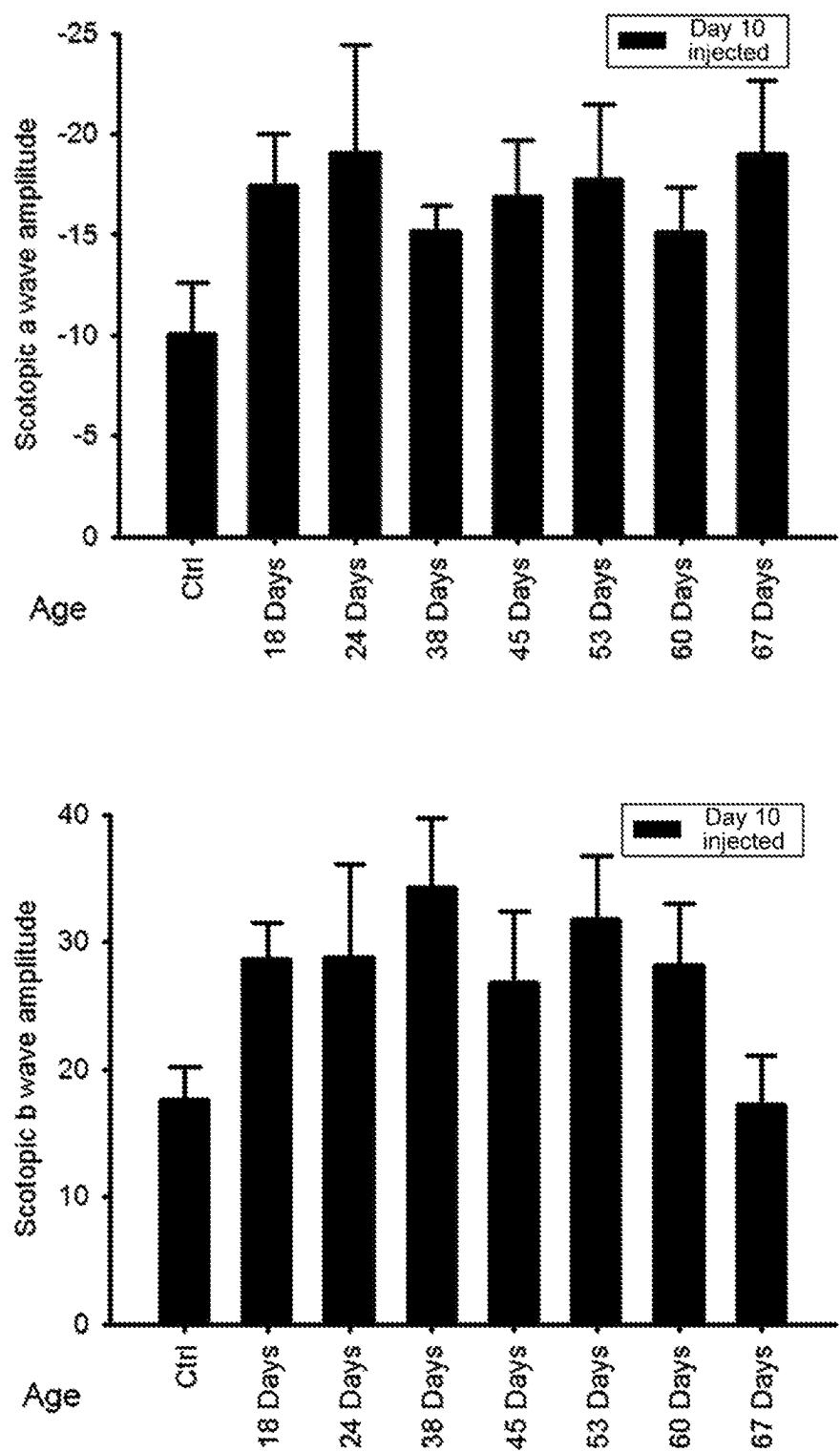


FIG. 13

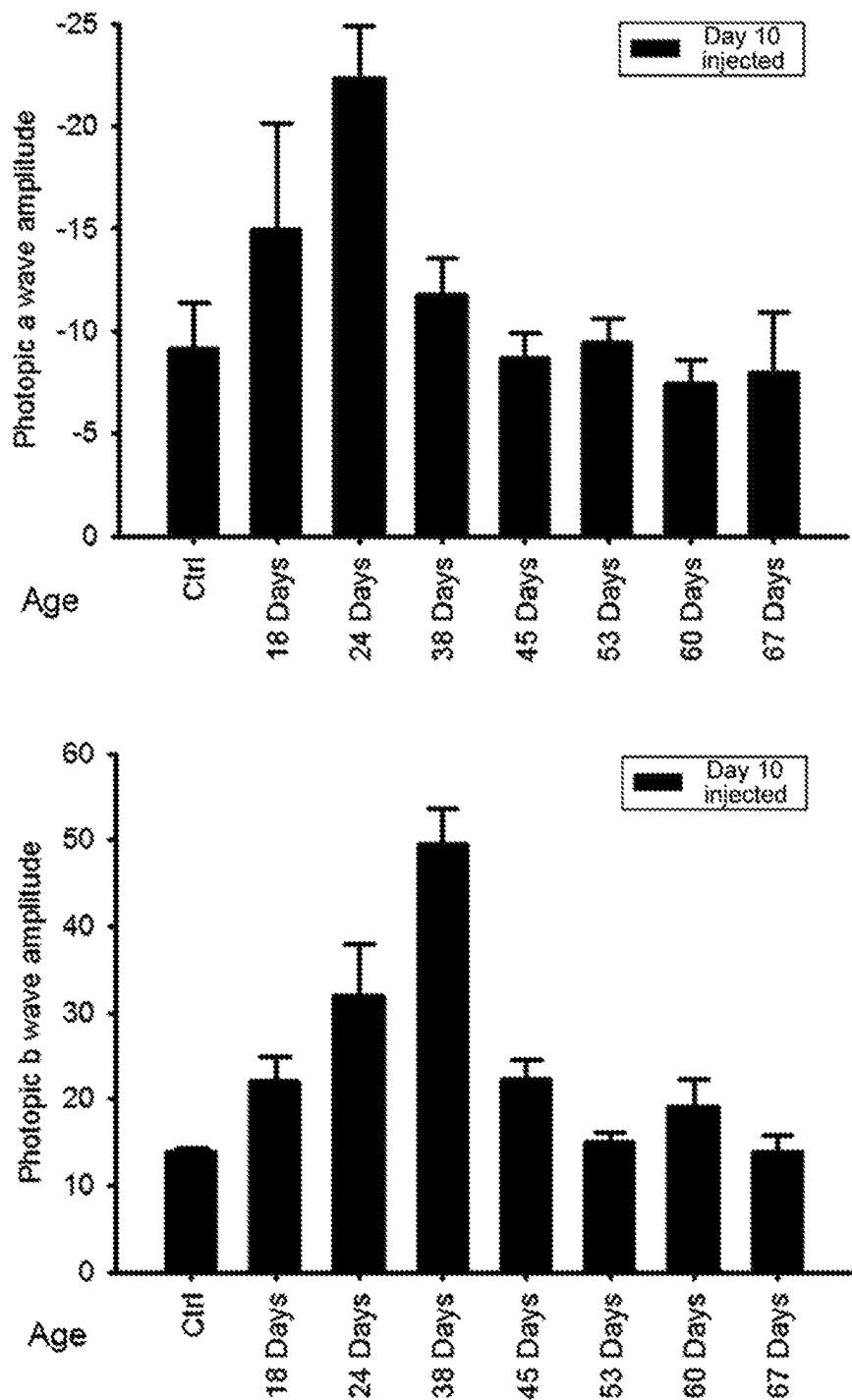


FIG. 14

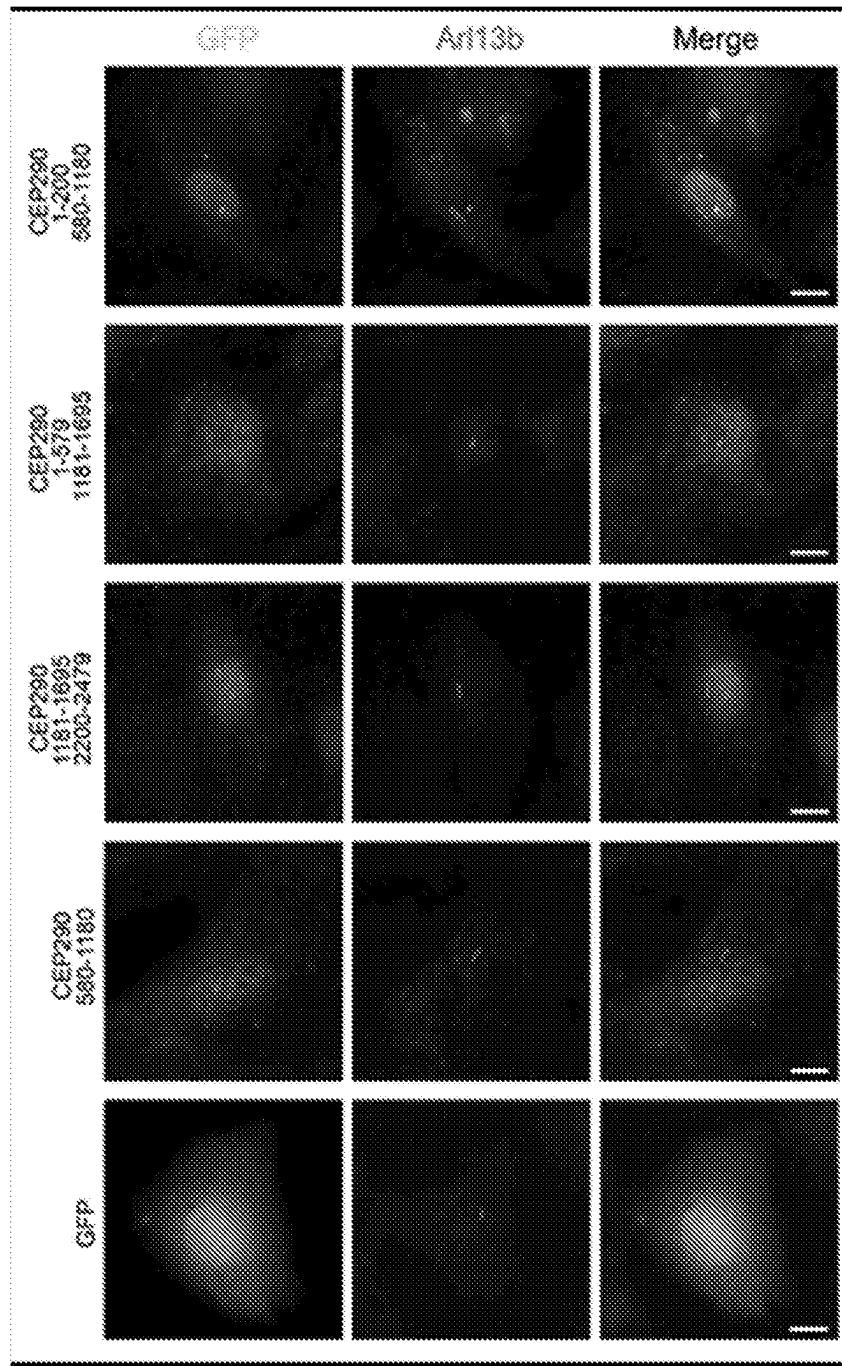


FIG. 15

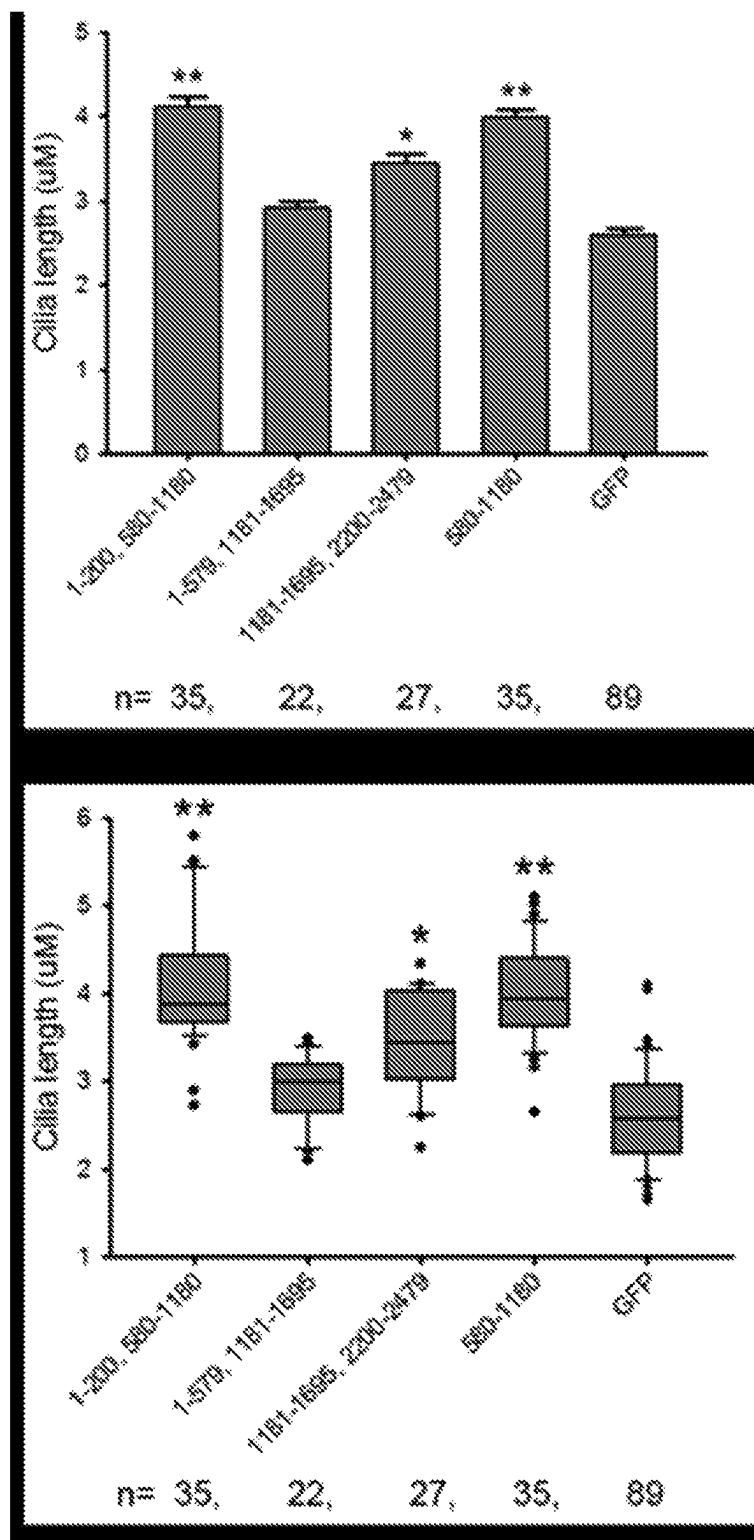


FIG. 16

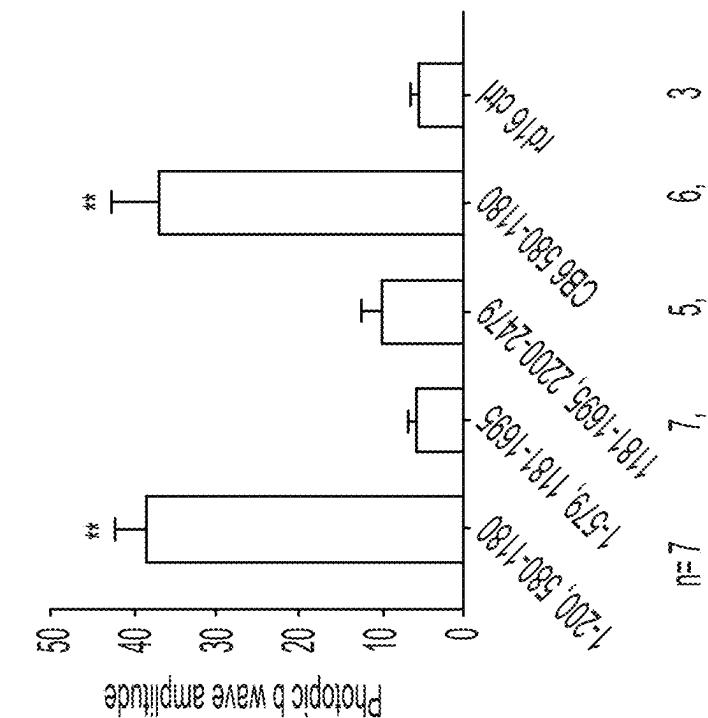


FIG. 17B

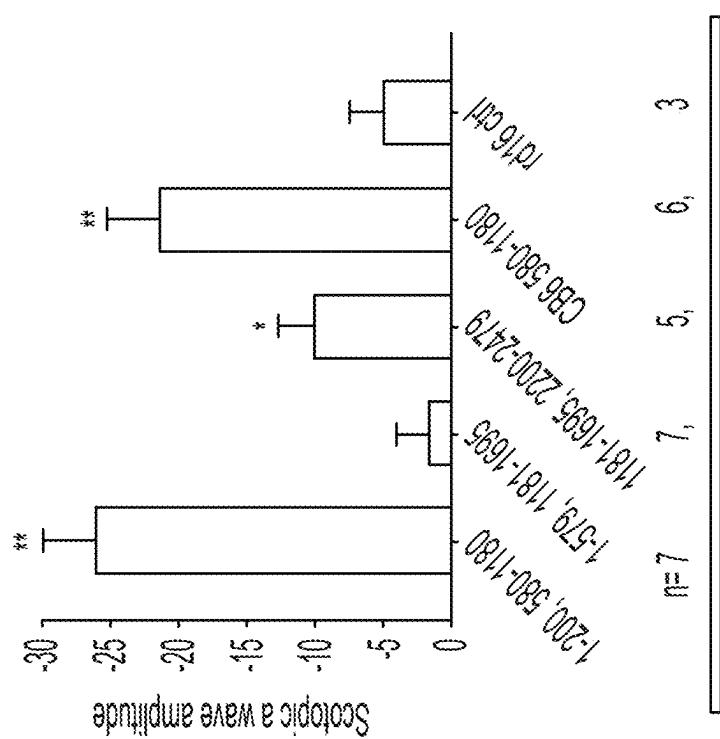


FIG. 17A

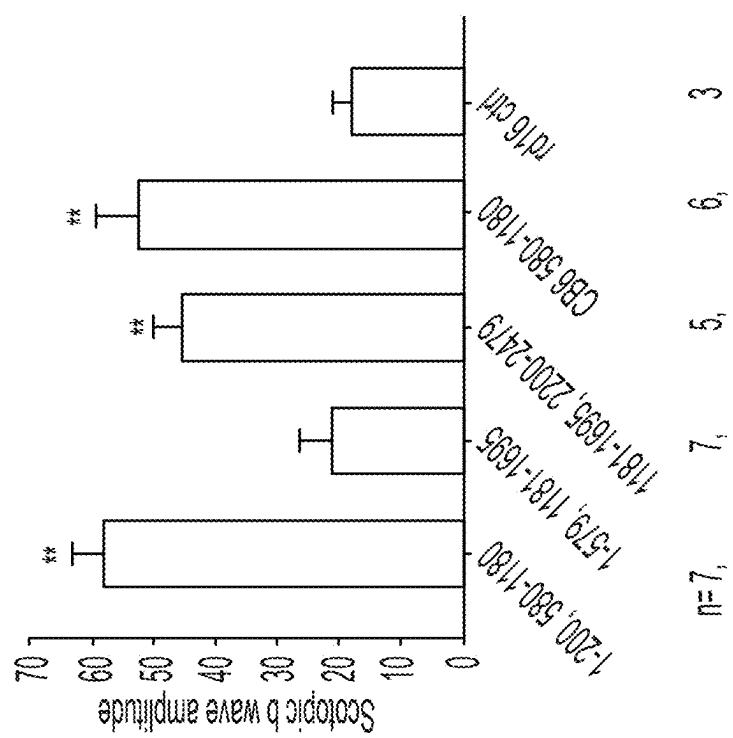


FIG. 17C

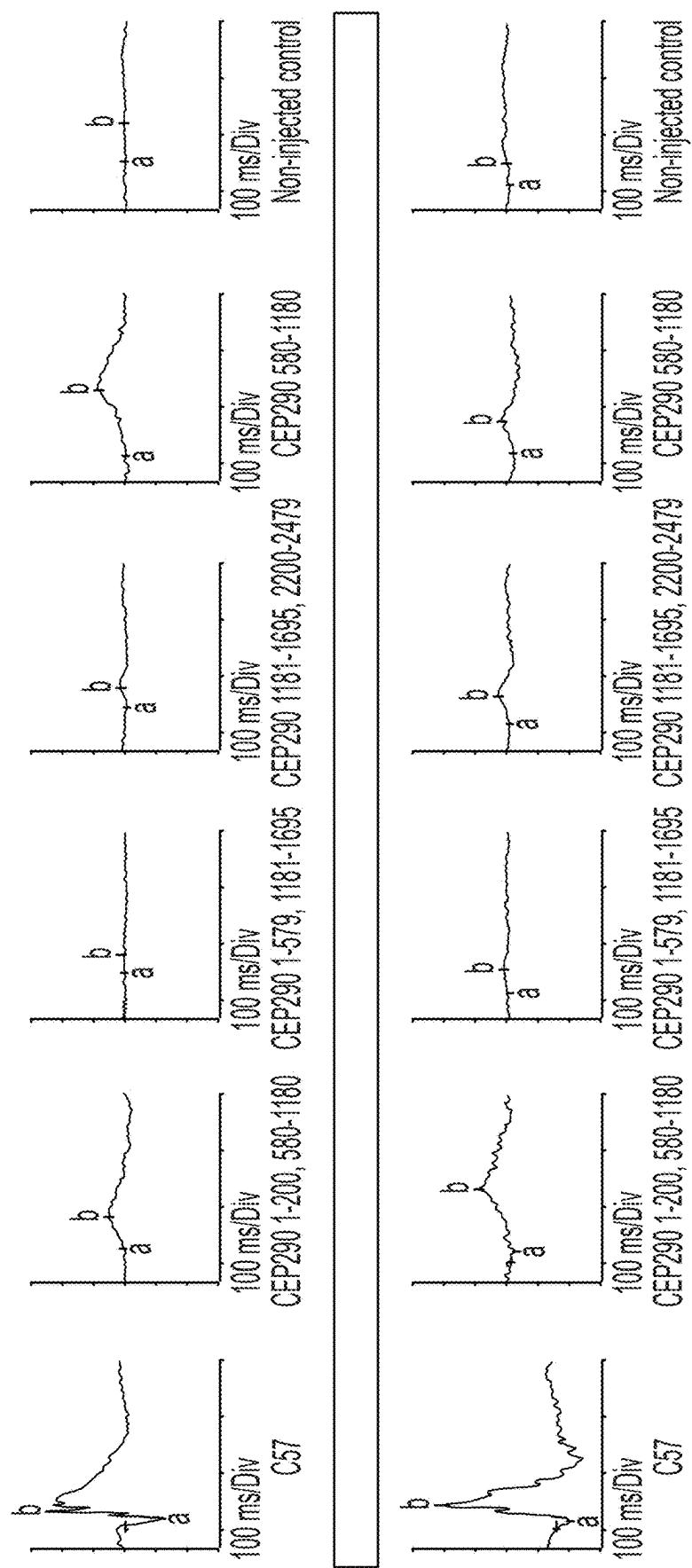


FIG. 17D

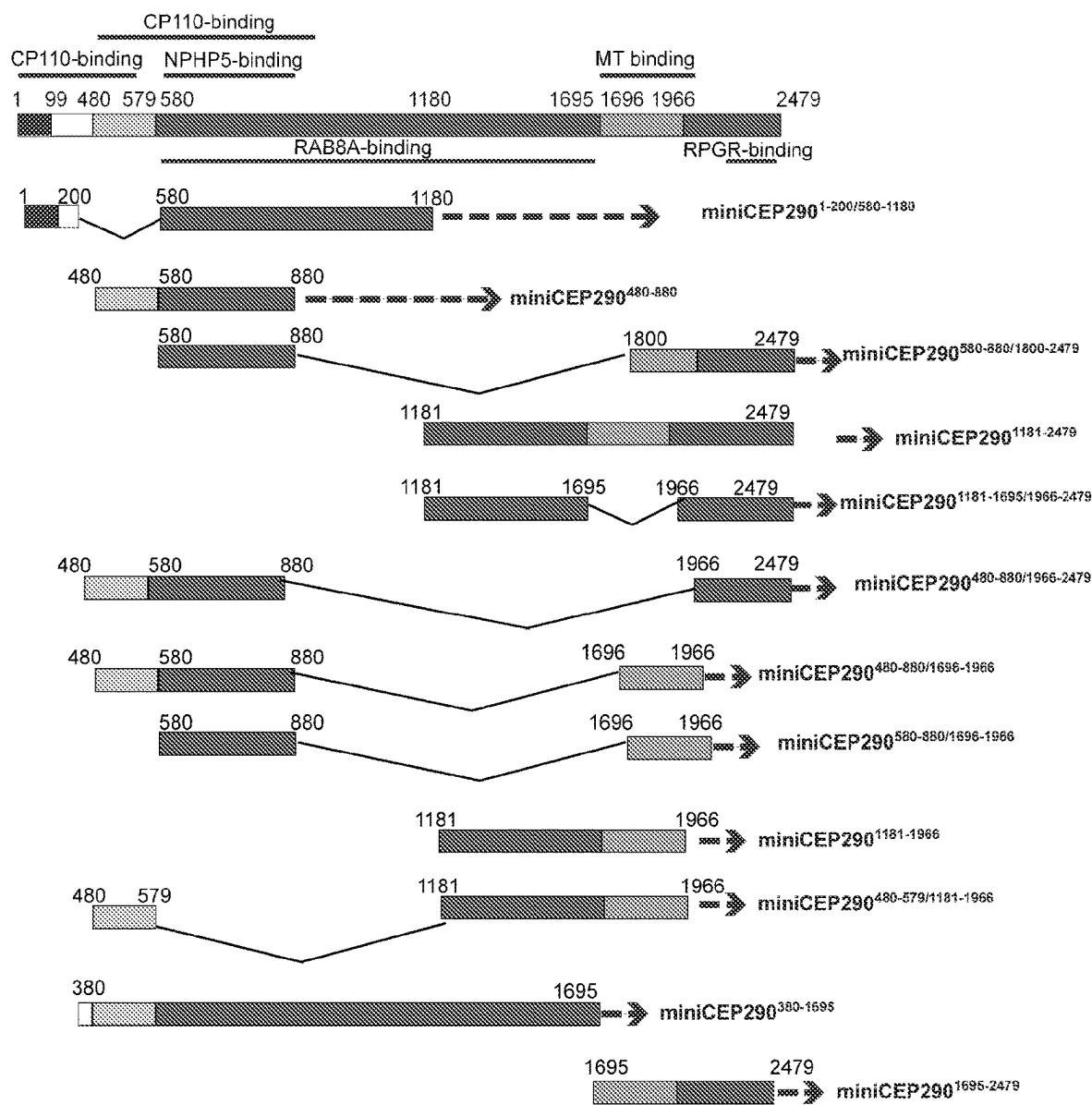


FIG. 18

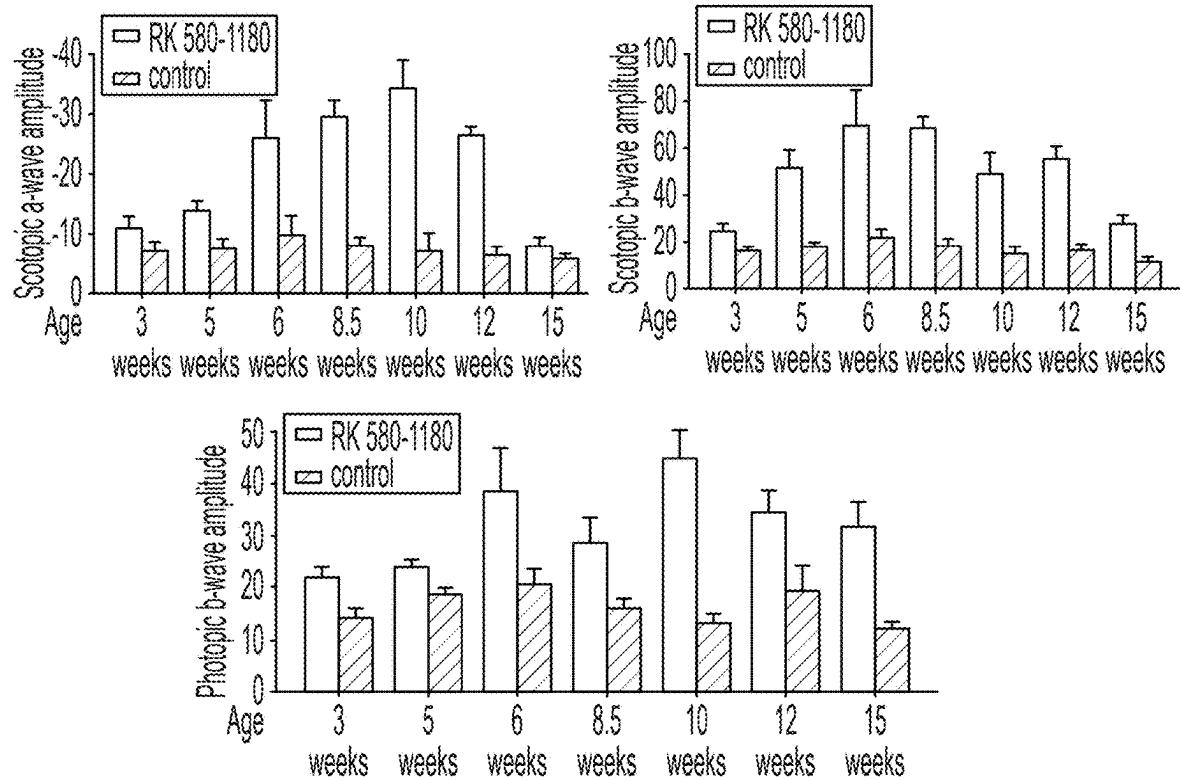


FIG. 19

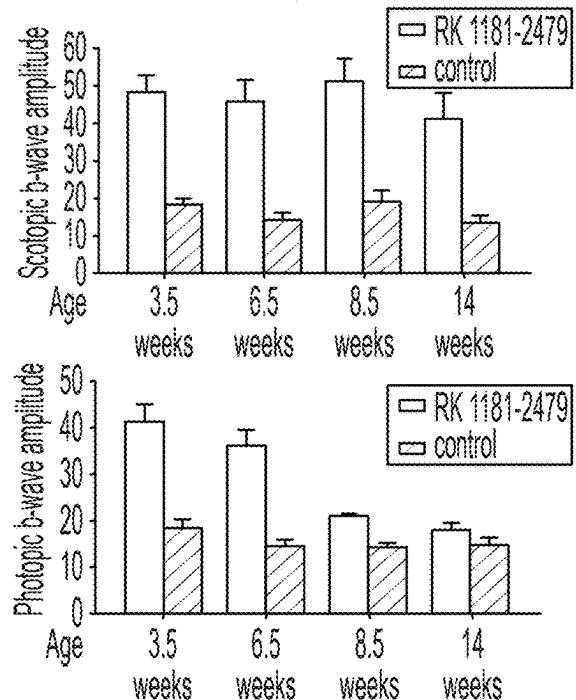


FIG. 20

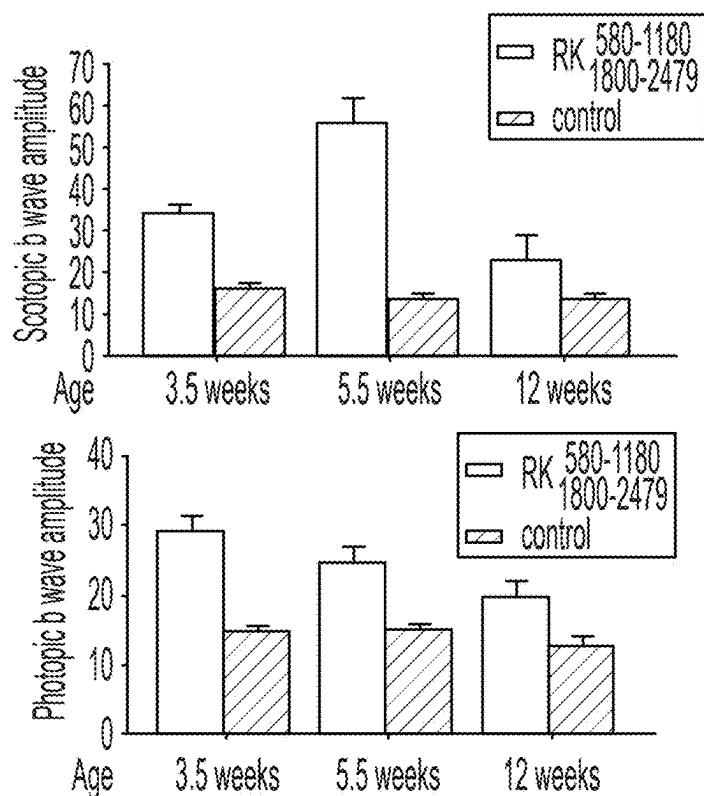


FIG. 21

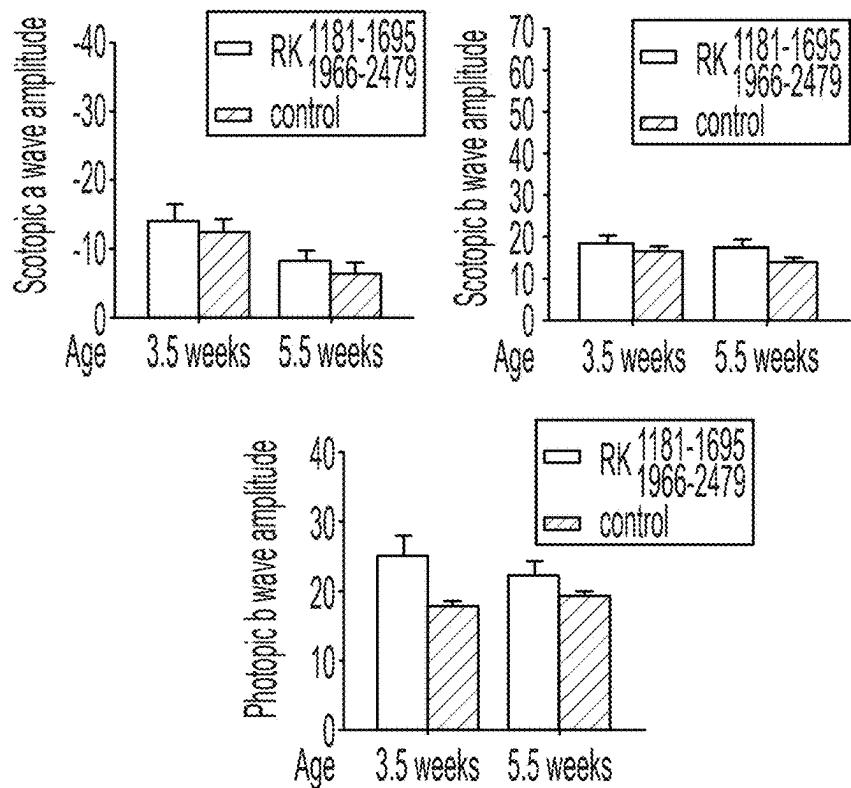


FIG. 22

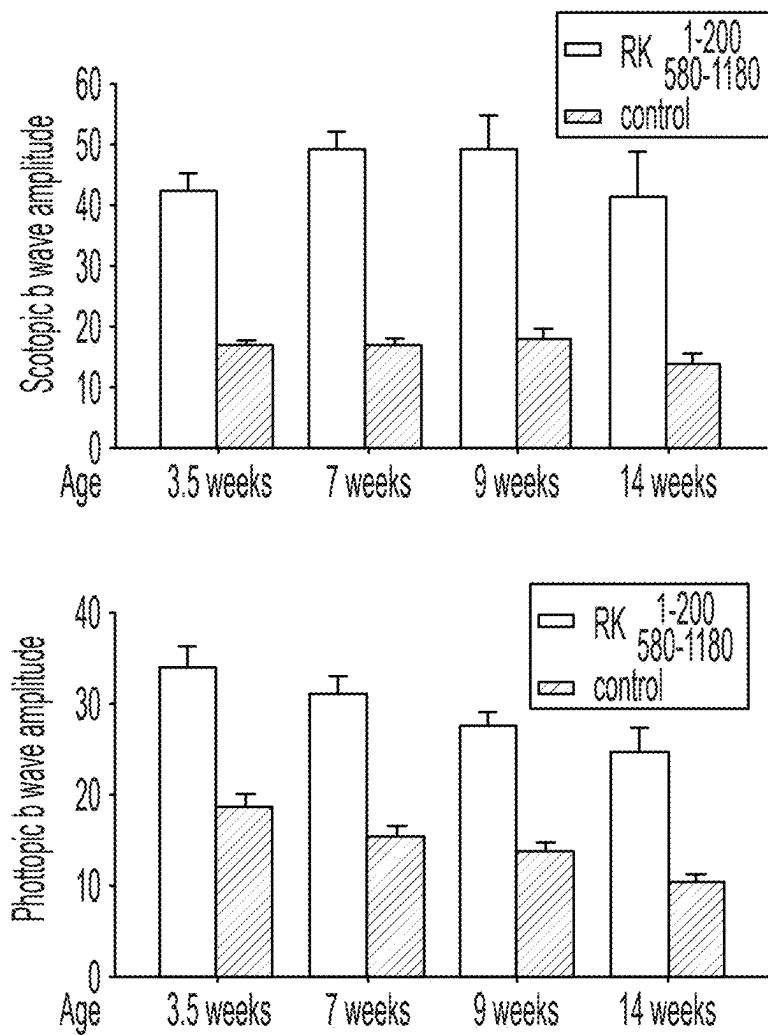
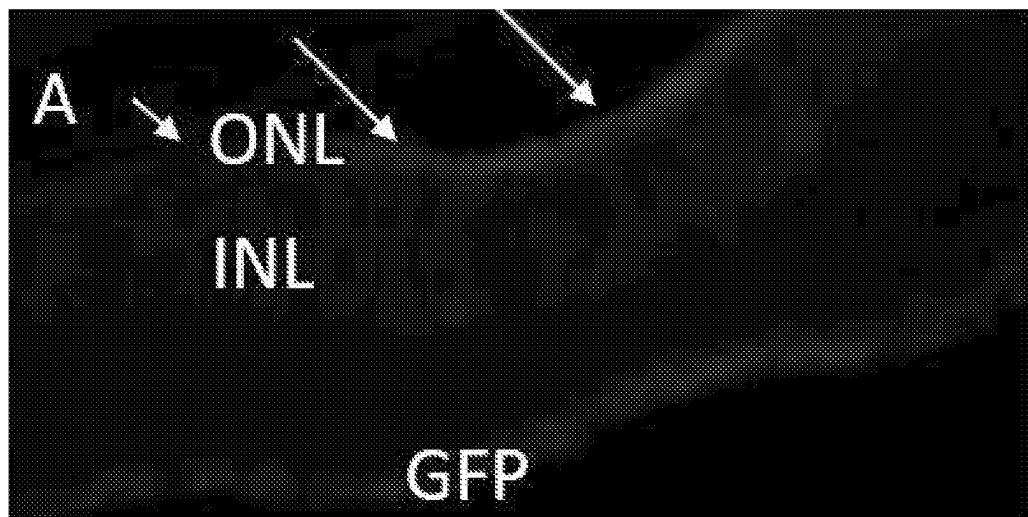
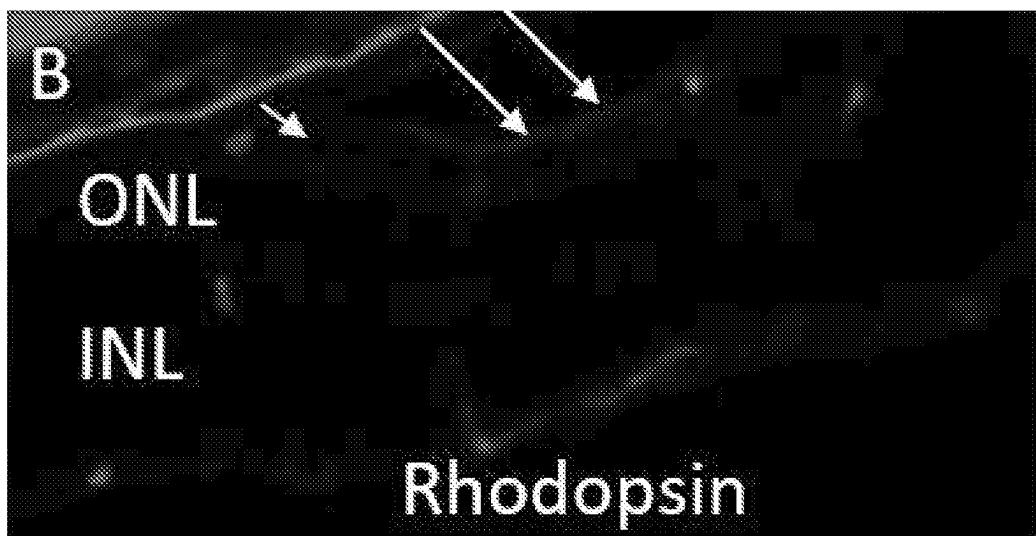


FIG. 23

FIG. 24A**FIG. 24B**

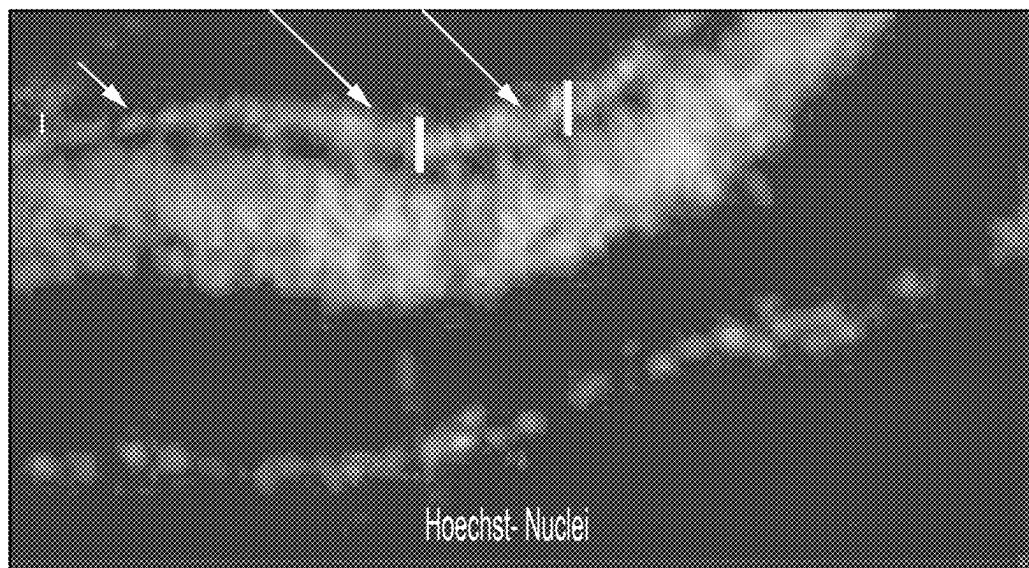


FIG. 24C

AAV-Human CEP290 1-200/580-1180 expression construct

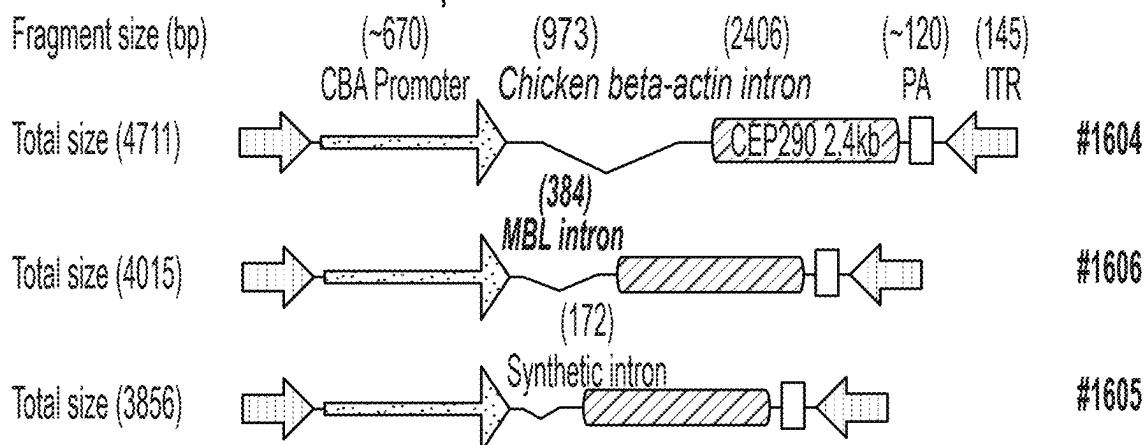


FIG. 25A

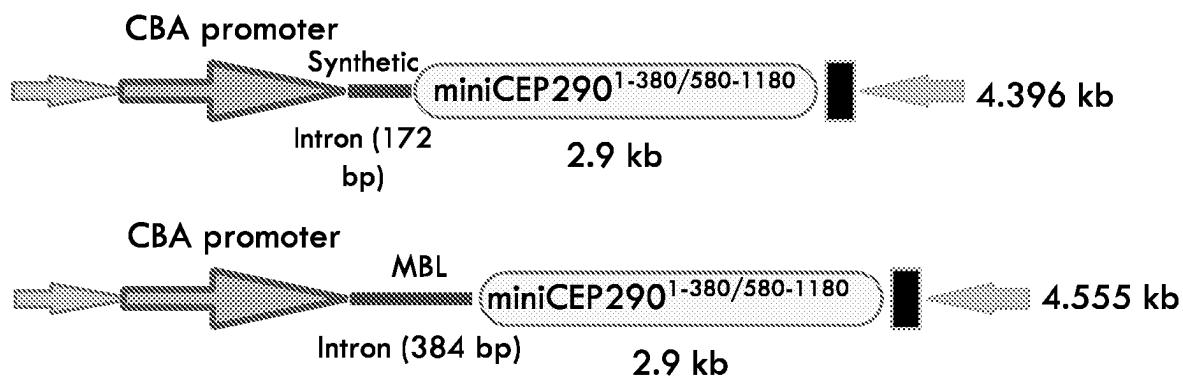
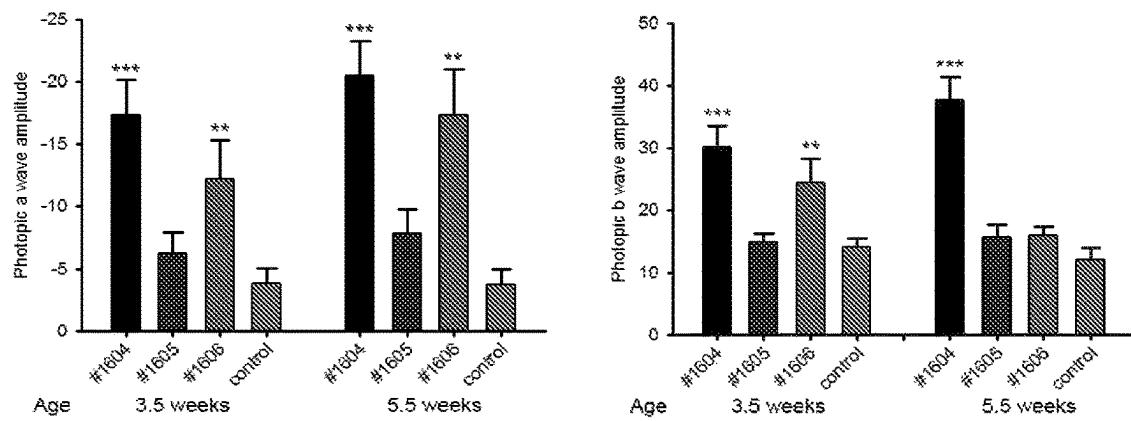
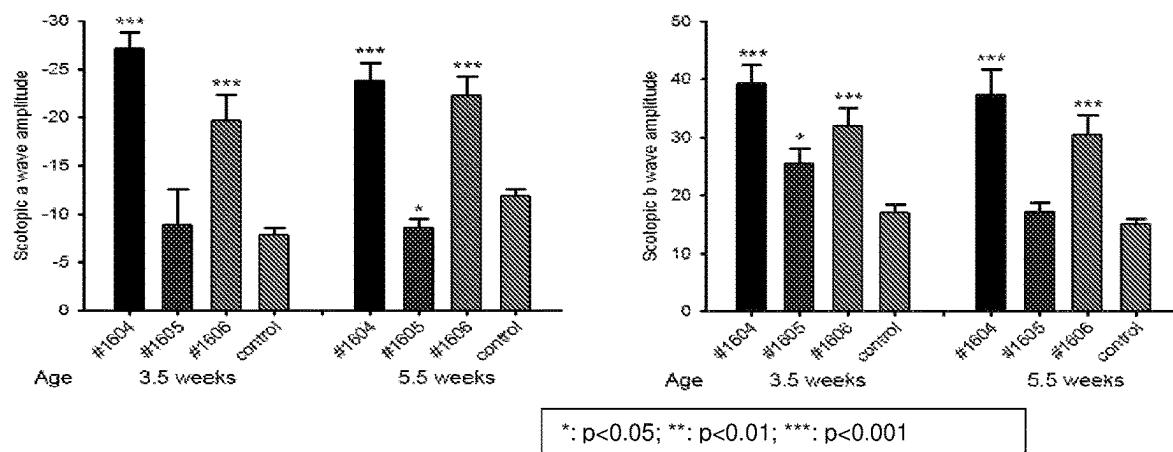
FIG. 25B

FIG. 25C

1**MINIGENE THERAPY****RELATED APPLICATIONS**

This application is a national stage filing under 35 U.S.C. § 371 of international PCT application PCT/US2020/033600, filed May 19, 2020, which claims the benefit under 35 U.S.C. § 119(e) of the filing date of U.S. provisional Application Ser. No. 62/967,521, filed Jan. 29, 2020, U.S. provisional Application Ser. No. 62/850,405, filed May 20, 2019, and U.S. provisional Application Ser. No. 62/899,601, filed Sep. 12, 2019, the entire contents of each application which are incorporated herein by reference.

GOVERNMENT SUPPORT

This invention was made with government support under EY022372, EY029050, NS076991, AI100263, and HL131471, awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Ciliopathies represent a group of diseases and disorders characterized by abnormal ciliary formation or function. For example ocular ciliopathies may lead to retinal degeneration, reduced visual acuity, and/or blindness. CEP290-associated Leber congenital amaurosis (LCA) is one of the most common and severe forms of retinal degenerative diseases. However, no treatment or cure currently exists. Generally, the large size of cilia-associated genes, for example the CEP290 gene (~8 kb), has limited the development of successful therapy using conventional Adeno-associated Viral (AAV) vector-mediated gene delivery approaches because the cargo size exceeds the ~4700 bp packaging limit of rAAVs. Use of genome editing (such as CRISPR/Cas9 approach) and antisense oligonucleotides can have off-target effects and are typically applicable to only one type of mutation in a cilia-associated gene. Accordingly, novel compositions and methods for treating ciliopathies are needed.

SUMMARY

Aspects of the disclosure relate to compositions and methods useful for delivering minigenes to a subject. Accordingly, the disclosure is based, in part, on gene therapy vectors, such as viral (e.g., rAAV) vectors, comprising one or more gene fragments encoding a therapeutic gene product, such as a protein or peptide (e.g., a minigene). In some aspects, a gene therapy vector further comprises one or more inhibitory nucleic acids that target an endogenous gene variant (e.g., mutant) that is associated with a disease or disorder (e.g., a gene associated with a ciliopathy). In some embodiments, the one or more inhibitory nucleic acids do not silence gene expression of the gene product encoded by the minigene. In some embodiments, methods are provided for treating ciliopathies (e.g., ocular ciliopathies), for example disorders and diseases characterized by a mutation or deletion of a cilia-associated gene, such as the CEP290 gene which is associated with Leber congenital amaurosis (LCA).

Accordingly, in some aspects, the disclosure relates to an isolated nucleic acid comprising a transgene encoding a CEP290 fragment having the amino acid sequence set forth in any one of SEQ ID NOs: 10-19 or 36.

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In some embodiments, a CEP290 fragment is encoded by a nucleic acid having the sequence set forth in any one of SEQ ID NOs: 20-29 and 34-35. In some embodiments, a CEP290 fragment is encoded by a nucleic acid having the sequence set forth in SEQ ID NO: 29 or 34. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising amino acids 1-200 and 580-1180 of a human CEP290. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising amino acids 1-200 and 580-1180 of SEQ ID NO: 1. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 19.

In some embodiments, a CEP290 fragment is encoded by a nucleic acid having the sequence set forth in SEQ ID NO: 35. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising amino acids 1-380 and 580-1180 of a human CEP290. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising amino acids 1-380 and 580-1180 of SEQ ID NO: 1. In some embodiments, a nucleic acid encodes a CEP290 protein fragment comprising or consisting of the amino acid sequence set forth in SEQ ID NO: 36.

In some embodiments, a transgene further comprises a promoter. In some embodiments, a promoter is a CB6 promoter, a CBA promoter, or a tissue-specific promoter. In some embodiments, a tissue specific promoter is an eye-specific promoter. In some embodiments, an eye-specific promoter is a retinoschisin promoter, K12 promoter, a rhodopsin promoter, a rod-specific promoter, a cone-specific promoter, a rhodopsin kinase promoter (e.g., a GRK1 promoter), or an interphotoreceptor retinoid-binding protein proximal (IRBP) promoter.

In some embodiments, a transgene further comprises an intron (e.g., a chicken-beta actin intron, a synthetic intron, MBL intron, etc.). In some embodiments, the intron is positioned between the promoter and minigene (e.g. Mini-CEP290) coding sequence of the transgene.

In some embodiments, a transgene is flanked by adeno-associated virus (AAV) inverted terminal repeats (ITRs). In some embodiments, AAV ITRs are AAV2 ITRs or a variant thereof, such as ΔITR or mITR ITRs.

In some aspects, the disclosure provides a vector comprising an isolated nucleic acid as described herein. In some embodiments, a vector is a plasmid.

In some aspects, the disclosure relates to a host cell comprising an isolated nucleic acid or a vector as described herein.

In some embodiments, the disclosure provides a recombinant adeno-associated virus (rAAV) comprising: a capsid protein; and, an isolated nucleic acid as described herein.

In some embodiments, a capsid protein is AAV8 capsid protein or AAV5 capsid protein. In some embodiments, a capsid protein is an AAV8 capsid protein or a variant thereof. In some embodiments, a capsid protein is an AAV5 capsid protein or a variant thereof. In some embodiments, a capsid protein comprises the amino acid sequence set forth in SEQ ID NO: 9.

In some embodiments, an rAAV is a self-complementary AAV (scAAV).

In some embodiments, an rAAV is formulated for delivery to the eye. In some embodiments, an rAAV is formulated for subretinal delivery. In some embodiments, an rAAV comprises one or more of the CEP290 fragments described by the disclosure and an AAV8 capsid protein or AAV5 capsid protein. In some embodiments, an rAAV comprises (i) a nucleic acid sequence encoding a CEP290 fragment com-

prising the amino acid sequence set forth in SEQ ID NO: 19 or 34 operably linked to a rhodopsin kinase (RK) promoter; and (ii) an rAAV8 capsid protein or AAV5 capsid protein. In some embodiments, the rAAV is formulated for subretinal delivery.

In some aspects, the disclosure provides a composition comprising an rAAV as described herein, and a pharmaceutically acceptable excipient. In some embodiments, a composition comprises a plurality of the rAAVs. In some embodiments, each rAAV of a plurality encodes a different CEP290 fragment.

In some aspects, the disclosure provides a method for treating an ocular ciliopathy in a subject in need thereof, the method comprising administering to a subject having an ocular ciliopathy a therapeutically effective amount of an isolated nucleic acid, rAAV, or composition as described herein.

In some embodiments, an ocular ciliopathy is associated with a mutation of the CEP290 gene in the subject or a deletion of a CEP290 gene in a subject. In some embodiments, a mutation in a CEP290 gene is an intronic mutation, a nonsense mutation, a frameshift mutation, a missense mutation, or any combination thereof. In some embodiments, the mutation or deletion of CEP290 results in retinal degeneration, photoreceptor degeneration, retinal dysfunction, and/or loss of vision.

In some embodiments, an ocular ciliopathy is Leber congenital amaurosis (LCA), Joubert syndrome, Bardet-Biedl syndrome, Meckel syndrome, Usher syndrome, Nephronophthisis, or Senior-Løken syndrome. In some embodiments, the ocular ciliopathy is Leber congenital amaurosis (LCA). In some embodiments such as Retinitis Pigmentosa (RP), the severity of an ocular ciliopathy is modified by CEP290.

In some embodiments, a subject is a human characterized by one or more CEP290 mutations (e.g., one or more mutations in a CEP290 gene) that occurs at position c.2991+1655. In some embodiments, at least one mutation is A1655G.

In some embodiments, administration of an isolated nucleic acid, rAAV, or composition results in delivery of a CEP290 fragment (e.g., a transgene encoding a CEP290 fragment) to the eye of a subject. In some embodiments, administration is via injection. In some embodiments, injection comprises subretinal injection or intravitreal injection. In some embodiments, administration is topical administration to the eye of the subject. In some embodiments, administration is by subretinal administration.

In some embodiments, an effective amount (e.g., administration of an effective amount of an isolated nucleic acid (messenger RNA), isolated CEP290 fragment protein, rAAV, or composition) results in photoreceptor (PR) function (e.g., increased PR function as measured by ERG). In some embodiments, an effective amount (e.g., administration of an effective amount of an isolated nucleic acid (messenger RNA), isolated CEP290 fragment protein, rAAV, or composition) results in photoreceptor (PR) function (e.g., increased PR function as measured by ERG), for up to fourteen weeks.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows schematic depiction of the full-length CEP290 gene representing the locations of distinct protein interaction domains.

FIG. 2A shows microscopy data relating to ciliary number and length in mouse embryonic fibroblasts (MEFs) from

wild-type (WT) and Cep290^{r^{d16}} mice that were serum-starved for 24 h (for cilia growth) and then stained with anti-acetylated α-tubulin antibody (cilia marker). The lower images depict higher magnification of cilia. FIG. 2B shows a statistically significant decrease in the length of cilia in mutant MEFs.

FIG. 3 shows Cep290^{r^{d16}} MEFs transfected with constructs encoding GFP or GFP-CEP290, followed by staining with ARL13b (cilia marker) and γ-tubulin. A significant increase in cilia length of cells expressing full-length CEP290 was observed. GFP-encoding construct was used as negative control. **: p<0.001.

FIG. 4A shows a schematic representation of the human CEP290 protein and deleted variants. Myo-tail: Myosin tail homology domain. Additional protein-interaction domains are also not shown. FIG. 4B shows immunoblot analysis using anti-GFP antibody of mouse fibroblasts transiently transfected with the constructs described in FIG. 4A. Specific protein bands (depicted by arrows) were detected indicating that the deleted variants are stably expressed in cells.

FIG. 5A shows immunostaining of Cep290^{r^{d16}} fibroblasts transiently transfected with plasmid encoding GFP-fused full-length (FL) CEP290 and indicated variants with GFP, γ-tubulin, ARL13B antibodies. Nuclei were stained with DAPI. Longer arrows indicate basal body/ciliary localization of the proteins whereas shorter arrows mark the diffuse staining. FIG. 5B shows cilia length of cells (n>200) described in FIG. 5A quantified using ImageJ. *: p<0.001. ns: not significant.

FIG. 6A shows immunoblot analysis of Cep290^{r^{d16}} fibroblasts transiently transfected with plasmid encoding GFP alone or GFP-fused indicated variants, using anti-GFP antibody. Arrows point to the expected size protein product. Molecular mass marker is shown in kDa. FIG. 6B shows immunostaining of the cells using GFP and ARL13B (cilia marker) antibodies. Nuclei were stained with DAPI. Arrows indicate basal body/ciliary localization of the proteins. FIG. 6C shows the cilia length of the cells (n>200) quantified using ImageJ. *: p<0.001.

Figs. 7A-7B show in vivo physiological rescue potential of miniCEP290^{s⁸⁰⁻¹¹⁸⁰}. FIG. 7A shows Cep290^{r^{d16}} mice subretinally injected at P0/P1 stage with indicated miniCEP290s or GFP, and analyzed by ERG at 3 weeks post injection. Age-matched uninjected WT or Cep290^{r^{d16}} (littermates) mice were used as controls for ERG. The ERG a-wave is represented by arrows while b-wave vis depicted using arrowheads. Data represent analysis of at least 6 mice. ***: p<0.0001; ns: not significant. FIG. 7B shows scotopic a-wave and b-wave amplitude for mice subretinally injected at P0/P1 stage with indicated miniCEP290s or GFP, and analyzed by ERG at 3 weeks post injection.

Figs. 8A-8D show in vivo morphological rescue of photoreceptors by miniCEP290^{s⁸⁰⁻¹¹⁸⁰}. FIG. 8A shows Cep290^{r^{d16}} retinas injected with indicated miniCEP290^{s⁸⁰⁻¹¹⁸⁰} or GFP stained with DAPI. FIG. 8B shows Cep290^{r^{d16}} retinas injected with indicated miniCEP290^{s⁸⁰⁻¹¹⁸⁰} or GFP assessed by ultrathin sectioning. ONL (outer nuclear layer) is marked with vertical lines. WT 60 retinal section is shown for comparison. INL: inner nuclear layer. FIG. 8C shows improved expression of RDS detected in the miniCEP290^{s⁸⁰⁻¹¹⁸⁰} injected Cep290^{r^{d16}} mice. GFP staining marks the injected regions. FIG. 8D shows retinal cryosections of Cep290^{r^{d16}} mice injected with the indicated 65 miniCEP290s were stained with GFP (injected regions), rhodopsin (RHO; rod-specific; or M-opsin (MOP; cone-specific) antibodies and DAPI (nuclei). Outer segment (OS)-

enriched opsin staining is detected in the miniCEP290⁵⁸⁰⁻¹¹⁸⁰-injected retinas. Dramatically reduced expression of opsins is detected in the miniCEP290²⁰³⁷⁻²⁴⁷⁹-injected retinas. ONL: outer nuclear layer; INL: inner nuclear layer; GCL: ganglion cell layer.

FIG. 9 shows additional embodiments of CEP290 minigenes.

FIG. 10 shows the cilia length of Cep290^{rd16} fibroblasts transiently transfected with plasmid encoding GFP alone or GFP-fused indicated variants, using anti-GFP antibody (n>200) quantified using ImageJ.

FIG. 11 shows Cep290^{rd16} mice subretinally injected at P0/P1 stage with indicated miniCEP290s or GFP, and analyzed by ERG at 3 weeks post injection. Age-matched uninjected WT or Cep290^{rd16} (littermates) mice were used as controls for ERG. The ERG a-wave is represented by arrows while b-wave vis depicted using arrowheads. Data represent analysis of at least 6 mice. ***: p<0.0001; ns: not significant.

FIG. 12 shows scotopic a-wave and b-wave amplitude for mice subretinally injected at P0/P1 stage with indicated miniCEP290s or GFP, and analyzed by ERG at 3 weeks post injection Scotopic (a- and b-waves) and photopic b-wave analysis of the injected mice performed at 4 and 5 weeks post injection and compared to the ERG at 3 weeks are shown. Age-matched uninjected WT and GFP-injected Cep290^{rd16} mice were used as controls.

FIG. 13 shows scotopic a-wave and b-wave amplitude for 10-day old mice subretinally injected with the indicated miniCEP290 construct (GRK-580-1180). ERG were recorded at the indicated days after injection.

FIG. 14 shows photopic a-wave and b-wave amplitude for 10-day old mice subretinally injected with the indicated miniCEP290 construct (GRK-580-1180). ERG were recorded at the indicated days after injection.

FIG. 15 shows micrographs of rd16 mouse embryonic fibroblasts transiently transfected with cDNA encoding the indicated minigenes and GFP.

FIG. 16 shows data for cilia length measurement of rd16 mouse embryonic fibroblasts transiently transfected with cDNA encoding the indicated minigenes encoding the protein and GFP.

FIGS. 17A-17D show scotopic and photopic wave amplitudes of CB6-promoter driving the indicated minigenes were subretinally injected into 10 day old rd16 mice. FIG. 17A shows scotopic a-wave amplitude. FIG. 17B shows photopic b-wave amplitude. FIG. 17C shows scotopic b-wave amplitude. FIG. 17D shows ERG of rd16 mice injected with CB6-1-200-580-1180 miniCEP290. ERG were recorded at indicated days after injection and compared to others.

FIG. 18 is a schematic depicting additional CEP290 minigenes.

FIG. 19 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-580-1180 in subretinally-injected mice. Rescue effect lasted more than 10 weeks post-injection.

FIG. 20 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1181-2479 in subretinally-injected mice. Rescue effect lasted up to 8.5 weeks post-injection.

FIG. 21 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-580-1180/1800-2479 in subretinally-injected mice. Rescue effect lasted up to 5.5 weeks post-injection.

FIG. 22 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1181-1695/1966-2479 in subretinally-injected mice.

5 FIG. 23 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1-200/580-1180 in subretinally-injected mice. Rescue effect lasted more than 14 weeks post-injection.

FIGS. 24A-24C show data from a morphological analysis 10 of Rhodopsin Kinase (RK) promoter driving miniCEP290-1-200/580-1180: the minigene was subretinally delivered with AAV8 at P10 stage to Cep290^{rd16} mice. The analysis was performed at 9 weeks of age. FIG. 24A shows miniCEP290-1-200/580-1180 immunofluorescence analysis of 15 the injected retinal region (GFP; longer arrows). FIG. 24B shows data indicating improvement in rhodopsin (longer arrows) after delivery of miniCEP290-1-200/580-1180. Shorter arrows do not show GFP expression (non-transduced) and consequently exhibit undetectable rhodopsin 20 expression. FIG. 24C shows nuclear staining data indicating more nuclear layers in the outer nuclear layer (ONL) region in the miniCEP290-1-200/580-1180-transduced area (longer arrows and longer vertical bars) as compared to the untransduced region (shorter arrow and shorter vertical bar).

25 FIGS. 25A-25C show codon optimized miniCEP290 constructs. FIG. 25A shows codon optimized miniCEP290 (1-200/580-1180) constructs with different promoters and introns. FIG. 25B shows codon optimized miniCEP290 (1-380/580-1180) constructs with different promoters and 30 introns. FIG. 25C shows representative data for codon optimized miniCEP290 (1-200/580-1180) constructs packaged into AAV5 capsid and injected subretinally into mice at P10 stage. The mice were then analyzed by ERG (both scotopic and photopic) at the ages indicated.

DETAILED DESCRIPTION

In some aspects, the disclosure relates to compositions and methods useful for treating certain genetic diseases, for 40 example monogenic diseases, ciliopathies, etc. Monogenic diseases are diseases that are diseases that result from abnormal expression or function of a single allele of a gene. Examples of monogenic diseases include but are not limited to thalassemia, sickle cell anemia, hemophilia, cystic fibrosis, Tay Sachs disease, Fragile X syndrome, Huntington's disease, etc. Ciliopathies are genetic disorders that affect the expression or function of cellular cilia, for example ocular ciliopathies. Examples of ciliopathies include but are not limited to Alstrom syndrome, Bardet-Biedl syndrome, Joubert syndrome, Merckel syndrome, nephronophthisis, orofaciocutaneous syndrome, Senior-Locken syndrome, polycystic kidney disease, primary ciliary dyskinesia, and situs inversus.

The disclosure is based, in part, on isolated nucleic acids, 55 vectors (e.g., plasmids, bacmids, etc.), and gene therapy vectors, such as viral (e.g., rAAV) vectors, comprising one or more gene fragments encoding a therapeutic gene product, such as a protein or peptide (e.g., a minigene), and optionally one or more inhibitory nucleic acids that target an endogenous gene variant (e.g., mutant) that is associated with a disease or disorder (e.g., a gene associated with a ciliopathy).

A gene therapy vector may be a viral vector (e.g., a lentiviral vector, an adeno-associated virus vector, etc.), a plasmid, a closed-ended DNA (e.g., cDNA), etc. In some embodiments, a gene therapy vector is a viral vector. In some embodiments, an expression cassette encoding a mini-

gene is flanked by one or more viral replication sequences, for example lentiviral long terminal repeats (LTRs) or adeno-associated virus (AAV) inverted terminal repeats (ITRs).

As used herein, “minigene” refers to an isolated nucleic acid sequence encoding a recombinant peptide or protein where one or more non-essential elements of the corresponding gene encoding the naturally-occurring peptide or protein have been removed and where the peptide or protein encoded by the minigene retains function of the corresponding naturally-occurring peptide or protein. A “therapeutic minigene” refers to a minigene encoding a peptide or protein useful for treatment of a genetic disease, for example, human centrosomal protein 290 (CEP290), dystrophin, dysferlin, Factor VIII, Amyloid precursor protein (APP), Tyrosinase (Tyr), etc. Minigenes are known in the art and are described, for example by Karpati and Acsadi (1994) *Clin Invest Med* 17(5):499-509; Plantier et al. (2001) *Thromb Haemost.* 86(2):596-603; and Xiao et al. (2007) *World J Gastroenterol.* 13(2):244-9.

Generally, an isolated nucleic acid encoding a minigene (e.g., a therapeutic minigene) is between about 10% and about 99% (e.g., about 10%, about 15%, about 20%, about 25%, about 30%, about 40% about 50%, about 60%, about 70%, about 75%, about 80%, about 90%, about 99%, etc.) truncated with respect to a nucleic acid sequence encoding the corresponding naturally-occurring wild-type protein. For example, in some embodiments, a minigene encoding a CEP290 protein fragment is about 76% truncated (e.g., comprises about 24% of the nucleic acid sequence) compared to a wild-type CEP290 gene.

Aspects of the disclosure relate to isolated nucleic acids comprising a transgene encoding one or more CEP290 fragments. A “fragment” refers to a protein encoded by at least two discontinuous nucleotide sequence portions that are in frame with each other and encode a functional protein. A CEP290 fragment may comprise an amino acid sequence corresponding to one or more domains of a CEP290 protein (e.g., SEQ ID NO: 1) or portions thereof, for example one or more of a CP110-binding domain (or a portion thereof), NPHP5-binding domain (or a portion thereof), RAB8A-binding domain (or a portion thereof), a microtubule (MT) binding domain (or a portion thereof), and a RPGR binding domain (or a portion thereof). In some embodiments, a CP110-binding domain corresponds to amino acid positions 1-579 of a wild-type CEP290 protein (e.g., SEQ ID NO: 1). In some embodiments, a NPHP5-binding domain corresponds to amino acid positions 580-880 of a wild-type CEP290 protein (e.g., SEQ ID NO: 1). In some embodiments, a RAB8A-binding domain corresponds to amino acid positions 580-1695 of a wild-type CEP290 protein (e.g., SEQ ID NO: 1). In some embodiments, a MT-binding domain corresponds to amino acid positions 1696-1966 of a wild-type CEP290 protein (e.g., SEQ ID NO: 1). In some embodiments, a RPGR-binding domain corresponds to amino acid positions 1966 to 2479 of a wild-type CEP290 protein (e.g., SEQ ID NO: 1).

In some embodiments, an isolated nucleic acid encodes a CEP290 fragment comprising the amino acid sequence set forth in any one of SEQ ID NOs: 10-19 and 36. In some embodiments, an isolated nucleic acid comprises the nucleic acid sequence set forth in any one of SEQ ID NOs: 20-29 and 34-35. In some embodiments, an isolated nucleic acid comprises a nucleic acid sequence that is at least 70%, 80%, 90%, 95%, or 99% identical to the nucleic acid sequence set forth in any one of SEQ ID NOs: 20-29 and 34-35.

In some embodiments, the nucleic acid encodes a CEP290 protein fragment corresponding to amino acids 1-200 and 580-1180 of human CEP290. In some embodiments, the nucleic acid encodes a CEP290 fragment comprising amino acids 1-200 and 580-1180 of SEQ ID NO: 1. In some embodiments, an isolated nucleic acid comprises the nucleic acid sequence set forth in SEQ ID NO: 29 or 34. In some embodiments, the nucleic acid encodes a CEP290 fragment corresponding to the amino acid sequence as set forth in SEQ ID NO: 19.

In some embodiments, the nucleic acid encodes a CEP290 protein fragment corresponding to amino acids 1-380 and 580-1180 of human CEP290. In some embodiments, the nucleic acid encodes a CEP290 fragment comprising amino acids 1-380 and 580-1180 of SEQ ID NO: 1. In some embodiments, an isolated nucleic acid comprises the nucleic acid sequence set forth in SEQ ID NO: 35. In some embodiments, the nucleic acid encodes a CEP290 fragment corresponding to the amino acid sequence as set forth in SEQ ID NO: 36.

In some embodiments, a nucleic acid sequence encoding a CEP290 fragment is codon-optimized. In some embodiments a codon-optimized CEP290 fragment is encoded by the nucleic acid sequence set forth in SEQ ID NO: 34 or 35. In some embodiments, a codon-optimized nucleic acid sequence encodes a CEP290 minigene comprising the amino acid sequence set forth in SEQ ID NO: 19 or 36.

In some embodiments, a nucleic acid comprises an expression cassette comprising the sequence set forth in SEQ ID NO: 29 or 34 (e.g., a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 19) operably linked to a promoter (e.g., a rhodopsin kinase (RK) promoter). In some embodiments, the expression cassette is flanked by adeno-associated virus (AAV) inverted terminal repeats (ITRs). In some embodiments, the ITRs are AAV2 ITRs. In some embodiments, the nucleic acid is encapsidated by one or more AAV capsid proteins. In some embodiments, the one or more AAV capsid proteins are AAV8 or AAV5 capsid proteins.

In some aspects, the disclosure relates to an isolated nucleic acids (e.g., vectors, such as viral vectors) comprising an expression cassette comprising a first isolated nucleic acid sequence encoding a therapeutic minigene and a second isolated nucleic acid sequence encoding one or more inhibitory nucleic acids, wherein the expression cassette is flanked by viral replication sequences, and wherein the one or more inhibitory nucleic acids do not bind to the isolated nucleic acid encoding the therapeutic minigene.

In some aspects, the disclosure relates to AAV-mediated delivery of CEP290 gene fragments (e.g. encoding CEP290 protein fragments) lacking the “M region” to cells (e.g., ocular cells) of a subject having a disease or disorder characterized by a mutation or deletion of the CEP290 gene, which restores or improves cilial length and rescues or improves photoreceptor function. This discovery is surprising in view of previous disclosures, for example US 2016/0185832, which describes that the “M region” of the CEP290 gene is necessary to mediate microtubule localization and cilium formation. In some embodiments, the Examples section of this disclosure describes domains (e.g., fragments) of CEP290 protein that retain function in photoreceptors and can be delivered using the conventional AAV vectors.

Accordingly, in some aspects, the disclosure provides an isolated nucleic acid comprising: a first region comprising a first adeno-associated virus (AAV) inverted terminal repeat (ITR), or a variant thereof; and, a second region comprising

a transgene encoding a CEP290 protein fragment, wherein the CEP290 protein fragment does not comprise amino acid positions 1695 to 1966 of SEQ ID NO: 1.

In some aspects, the disclosure provides an isolated nucleic acid comprising: a first region comprising a first adeno-associated virus (AAV) inverted terminal repeat (ITR), or a variant thereof; and, a second region comprising a transgene encoding a CEP290 protein fragment, wherein the CEP290 protein fragment comprises at least 500 contiguous amino acids of SEQ ID NO: 1. In some embodiments, the at least 500 contiguous amino acids comprises or consists of a sequence selected from SEQ ID NOs: 2, 3 and 4.

In some embodiments, the second region does not comprise amino acid positions 1695 to 1966 of SEQ ID NO: 1. In some embodiments, the transgene comprises no more than 1120 contiguous amino acids of SEQ ID NO: 1.

In some embodiments, the transgene comprises amino acid positions 580 to 1695 of SEQ ID NO: 1. In some embodiments, the CEP290 protein fragment encoded by the transgene comprises a sequence set forth in SEQ ID NO: 2. In some embodiments, the CEP290 protein fragment encoded by the transgene comprises amino acid positions 580 to 1180 of SEQ ID NO: 1, or amino acid positions 1181 to 1695 of SEQ ID NO: 1. In some embodiments, the CEP290 protein fragment encoded by the transgene comprises or consists of a sequence set forth in SEQ ID NO: 3 or 4. In some embodiments, the CEP290 protein fragment encoded by the transgene comprises (or consists of) amino acid positions 1 to 200 of SEQ ID NO: 1 and amino acid positions 580 to 1180 of SEQ ID NO: 1. In some embodiments, the CEP290 protein fragment encoded by the transgene comprises or consists of a sequence set forth in SEQ ID NO: 29 or 34. It should be appreciated that CEP290 protein fragments delivered by the transgene may be translated as a single fusion protein comprising two or more fragments, or as separate polypeptides.

In some embodiments, the transgene comprises or consists of a nucleic acid sequence selected from SEQ ID NO: 5, 6 and 7.

In some embodiments, a gene therapy vector further comprises one or more inhibitory nucleic acids that do not silence gene expression of the gene product encoded by the minigene but do silence gene expression of an endogenous protein corresponding to a wild-type or disease-associated variant of the protein encoded by the minigene. For example, in some embodiments, a gene therapy vector comprises a minigene encoding a CEP290 protein fragment and one or more inhibitory nucleic acids (e.g., dsRNA, siRNA, shRNA, miRNA, amiRNA, etc.) that inhibit expression of endogenously expressed CEP290 (e.g., a CEP290 mutant selected from c.2991+1655A>G, c.2249T>G, c.7341dupA, c.2118_2122dupTCAGG, c.3814C>T, c.679_680delGA, c.265dupA, c.180+1G?T, c.1550delT, c.4115_4116delTA, c.4966G>T, and c.5813_5817delCTTTA) but do not inhibit expression of the CEP290 fragment encoded by the minigene. The skilled artisan will also appreciate that, in some embodiments, one or more inhibitory nucleic acids that inhibit expression of endogenously expressed CEP290 but do not inhibit expression of the CEP290 fragment encoded by the minigene may be administered to a subject in a manner that is separate from the gene therapy construct.

In some aspects, the CEP290 fragment is encoded by the messenger RNA. In other aspects, the CEP290 fragment is the protein delivered to the affected cells. In some embodiments one or more CEP290 fragments is delivered to

affected cells by a nanoparticle or microsphere-based delivery system. In some embodiments, a nanoparticle or microsphere-based delivery system is formulated to penetrate the affected cell, for example via inclusion of a cell permeable peptide (cpp) sequence to the CEP290 fragment(s) or delivery system (e.g., nanoparticle).

Methods for Treating Ocular Ciliopathies

Aspects of the invention relate to certain protein-encoding transgenes (e.g., fragments of human CEP290) that when delivered to a subject are effective for promoting growth of ocular cilia (e.g., cilia of photoreceptors) and rescue of photoreceptor structure and function in the subject. Accordingly, methods and compositions described by the disclosure are useful, in some embodiments, for the treatment of ocular ciliopathies associated with mutations or deletions of CEP290 gene, such as Leber congenital amaurosis (LCA), Joubert syndrome, Bardet-Biedl syndrome, Meckel syndrome, Usher syndrome, and Senior-Løken syndrome.

As used herein “treat” or “treating” refers to (a) preventing or delaying onset of ocular ciliopathies associated with mutations or deletions of CEP290 gene (such as Leber congenital amaurosis (LCA), Joubert syndrome, Bardet-Biedl syndrome, Meckel syndrome, Usher syndrome, or Senior-Løken syndrome); (b) reducing severity of ocular ciliopathies associated with mutations or deletions of CEP290 gene; (c) reducing or preventing development of symptoms characteristic of ocular ciliopathies associated with mutations or deletions of CEP290 gene; (d) and/or preventing worsening of symptoms characteristic of ocular ciliopathies associated with mutations or deletions of CEP290 gene. Signs and symptoms of ocular ciliopathies associated with mutations or deletions of CEP290 gene include, for example, photoreceptor degeneration, impairment of photoreceptor function, cell death, etc.

Methods for delivering a transgene (e.g., a gene encoding a CEP290 protein or a fragment thereof) to a subject are provided by the disclosure. The methods typically involve administering to a subject an effective amount of an isolated nucleic acid encoding a CEP290 protein fragment, or a rAAV comprising a nucleic acid for expressing a CEP290 protein fragment.

The human CEP290 gene consists of 52 exons, which encode for a protein of ~290 kDa (2479 amino acids). In some embodiments, the human CEP290 gene encodes a protein comprising the amino acid sequence set forth in SEQ ID NO: 1, and as described as GenBank Accession Number (NP_079390.3). In some embodiments, the human CEP290 gene (e.g., NCBI Reference Sequence: NM_025114.3) comprises a sequence set forth in SEQ ID NO: 8.

CEP290 is a multidomain protein and contains numerous coiled-coil domains distributed over the entire length of the protein. In addition, the CEP290 protein contains membrane and microtubule-binding domains and myosin-tail homology domain. Typically, CEP290 predominantly localizes to the centrosomes and transition zone of primary cilia and to the CC of photoreceptors. Previous publications have observed that the domain of CEP290 that localizes the protein to centrosomes (e.g., the “M region” of the CEP290 gene, as described in US 2016/0185832) is necessary to mediate microtubule localization and cilium formation. In some embodiments, the “M region” refers to amino acid residues 1695 to 1966 of human CEP290, as described in US 2016/0185832.

Aspects of the instant disclosure are based, in part, on the surprising discovery that certain CEP290 fragments lacking the “M” region mediate effective rescue of ciliary formation

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and photoreceptor rescue when expressed in a subject in need thereof, for example via administration of a viral vector (e.g., rAAV).

Accordingly in some aspects, the disclosure provides a transgene encoding a CEP290 protein fragment, wherein the CEP290 protein fragment does not comprise amino acid positions 1695 to 1966 (e.g., a region encompassing the “M” region) of SEQ ID NO: 1. A “CEP protein fragment” refers to a 2 to 2479 (e.g., any integer between 2 and 2479) amino acid portion of a CEP290 protein. In some embodiments, the CEP protein fragment comprises a contiguous amino acid portion (e.g., amino acids 580 to 1180) of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, the CEP protein fragment comprises one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) interrupted amino acid portions (e.g., amino acids 1 to 10, 580 to 1180 and 1967 to 2470) of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP protein fragment comprises a methionine (M) amino acid residue at its N-terminus.

In some embodiments, the CEP290 protein fragment comprises at least 500 contiguous amino acids of SEQ ID NO: 1. For example, in some embodiments, the CEP290 protein fragment comprises (or consists of) amino acids 580 to 1695, or amino acids 580 to 1180, or amino acids 1181 to 1695, of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, the at least 500 contiguous amino acids comprises or consists of a sequence selected from SEQ ID NOS: 2, 3 and 4.

In some embodiments, a CEP290 protein comprises amino acids 480 to 579 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein fragment comprises amino acids 480 to 580 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 480 to 880 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 580 to 880 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 580 to 1180 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 1181 to 1695 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 1181 to 1966 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 1181 to 2479 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 1696 to 1966 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 protein comprises amino acids 1966 to 2479 of CEP290 (e.g., SEQ ID NO: 1). In some embodiments, a CEP290 fragment comprises two or more (e.g., 2, 3, 4, 5, 6, or more) of the foregoing fragments. In some embodiments, a CEP290 fragment comprises two or more (e.g., 2, 3, 4, 5, 6, or more) of the foregoing fragments that are not contiguous in SEQ ID NO: 1. In some embodiments, a CEP290 protein fragment comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOS: 10-19. In some embodiments, a CEP290 protein comprises amino acids 1-200 and 580-1180 of human CEP290. In some embodiments, a CEP290 protein comprises amino acids 1-200 and 580-1180 of SEQ ID NO: 1. In some embodiments, a CEP290 protein comprises the amino acid sequence set forth in SEQ ID NO: 19. In some embodiments, a CEP290 protein is encoded by the nucleic acid sequence set forth in SEQ ID NO: 29 or 34. In some embodiments, a CEP290 protein comprises amino acids 1-380 and 580-1180 of human CEP290. In some embodiments, a CEP290 protein

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comprises amino acids 1-380 and 580-1180 of SEQ ID NO: 1. In some embodiments, a CEP290 protein comprises the amino acid sequence set forth in SEQ ID NO: 36. In some embodiments, a CEP290 protein is encoded by the nucleic acid sequence set forth in SEQ ID NO: 35.

In some embodiments, the disclosure provides a transgene comprising a nucleic acid (e.g., isolated nucleic acid) encoding a CEP290 protein fragment. In some embodiments, the transgene comprises or consists of a nucleic acid sequence selected from SEQ ID NO: 5, 6 and 7. In some embodiments, the transgene comprises or consists of a nucleic acid sequence selected from any one of SEQ ID NOS: 20-29.

In some embodiments, the transgenes encoding a CEP290 fragment described by the disclosure mediate ciliary growth and photoreceptor rescue, and are therefore useful for treating ciliopathies, for example ocular ciliopathies. Generally, a “ciliopathy” refers to a disease or disorder characterized by defective (or lack of) protein function resulting in abnormal formation or function of cilia in a cell of a subject. An “ocular ciliopathy” is a ciliopathy where abnormal formation or function of cilia occurs in ocular cells (e.g., rods, cones, photoreceptor cells, etc.) of a subject, typically resulting in retinal degeneration, loss of vision and blindness. Examples of ciliopathies include but are not limited to earlier onset developmental anomalies such as Meckel Gruber Syndrome and Joubert Syndrome, to relatively later onset diseases, such as Bardet-Biedl Syndrome, Senior-Loken Syndrome, and Usher Syndrome. In some embodiments, retinal dystrophies (e.g., due to an ocular ciliopathy) are more commonly presented in a non-syndromic manner.

In some embodiments, the ocular ciliopathy is Leber congenital amaurosis (LCA). Generally, LCA is a clinically and genetically heterogeneous disease with early onset severe retinal degeneration starting either at birth or by 5-7 years of age. In some embodiments, the LCA is LCA1, LCA2, LCA3, LCA4, LCA5, LCA6, LCA7, LCA8, LCA9, LCA10, LCA11, LCA12, LCA13, LCA14, LCA15, LCA16, or LCA17. In some embodiments, the LCA is LCA10 (e.g., LCA associated with one or more mutations in a CEP290 gene). Generally, a mutation or mutations in CEP290 account for >26% of LCA (LCA10; OMIM 611755). In some embodiments, LCA is characterized by a deletion of the CEP290 gene in a subject. Generally, a mutation in CEP290 that results in LCA may be an intronic mutation, a nonsense mutation, a frameshift mutation, a missense mutation, or any combination thereof. Examples of CEP290 gene mutations associated with LCA include but are not limited to c.2991+1655A>G, c.2249T>G, c.7341dupA, c.2118_2122dupTCAGG, c.3814C>T, c.679_680delGA, c.265dupA, c.180+1G?T, c.1550delT, c.4115_4116delTA, c.4966G>T, and c.5813_5817delCTTTA, for example as described by den Hollander et al. (2006) Am J Hum Genet. 79(3):556-561. In some embodiments, the mutation in CEP290 is a deep intronic mutation, for example at position c.2991+1655A. In some embodiments, the deep intronic mutation is c.2991+1655A>G. In some embodiments, the severity of an ocular ciliopathy is modified by CEP290 mutations. For example, as described in Rao et al. (2016). Hum Mol Genet, 25(10):2005-2012. Deletions and/or mutations in a CEP290 gene of a subject (e.g., a subject having or suspected of having a ciliopathy associated with a deletion or mutation of CEP290 gene) may be identified from a sample obtained from the subject (e.g., a DNA sample, RNA sample, blood sample, or other biological sample) by any method known in the art. For example, in some embodiments, a nucleic acid (e.g., DNA, RNA, or a combination thereof) is extracted from a biological samples obtained

from a subject and nucleic acid sequencing is performed in order to identify a mutation in the CEP290 gene. Examples of nucleic acids sequencing techniques include but are not limited to Maxam-Gilbert sequencing, pyrosequencing, chain-termination sequencing, massively parallel signature sequencing, single-molecule sequencing, nanopore sequencing, Illumina sequencing, etc. In some embodiments, a mutation or deletion in CEP290 gene is detected indirectly, for example by quantifying CEP290 protein expression (e.g., by Western blot) or function (e.g., by analyzing ciliary growth, structure, function, etc.), or by direct sequencing of the DNA and comparing the sequence obtained to a control DNA sequence (e.g., a wild-type CEP290 DNA sequence).

In some aspects, the disclosure provides a method for treating an ocular ciliopathy in a subject in need thereof, the method comprising administering to a subject having an ocular ciliopathy a therapeutically effective amount of an isolated nucleic acid, or a rAAV, as described by the disclosure. In some embodiments, the administration is sub-retinal administration.

An “effective amount” of a substance is an amount sufficient to produce a desired effect. In some embodiments, an effective amount of an isolated nucleic acid (e.g., an isolated nucleic acid comprising a transgene encoding a CEP290 protein fragment as described herein) is an amount sufficient to transfect (or infect in the context of rAAV mediated delivery) a sufficient number of target cells of a target tissue of a subject. In some embodiments, a target tissue is ocular tissue (e.g., photoreceptor cells, rod cells, cone cells, retinal ganglion cells, retinal cells, retinal pigmented epithelial cells, etc.). In some embodiments, an effective amount of an isolated nucleic acid (e.g., which may be delivered via an rAAV) may be an amount sufficient to have a therapeutic benefit in a subject, e.g., to increase or supplement the expression of a gene or protein of interest (e.g., CEP290), to improve in the subject one or more symptoms of disease (e.g., a symptom of an ocular ciliopathy, such as LCA), etc., such as light perception, photoreceptor function (electroretinography) and structure of the retina. The effective amount will depend on a variety of factors such as, for example, the species, age, weight, health of the subject, and the tissue to be targeted, and may thus vary among subject and tissue as described elsewhere in the disclosure.

Isolated Nucleic Acids

In some aspects, the disclosure provides isolated nucleic acids that are useful for expressing human CEP290, or a fragment thereof. A “nucleic acid” sequence refers to a DNA or RNA sequence. In some embodiments, proteins and nucleic acids of the disclosure are isolated. As used herein, the term “isolated” means artificially produced. As used herein with respect to nucleic acids, the term “isolated” means: (i) amplified in vitro by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulable by recombinant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the material in the cell in which it resides.

Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulable by standard techniques known to those of ordinary skill in the art. As used herein with respect to proteins or peptides, the term “isolated” refers to a protein or peptide that has been isolated from its natural environment or artificially produced (e.g., by chemical synthesis, by recombinant DNA technology, etc.).

The skilled artisan will also realize that conservative amino acid substitutions may be made to provide functionally equivalent variants, or homologs of the capsid proteins. In some aspects the disclosure embraces sequence alterations that result in conservative amino acid substitutions. As used herein, a conservative amino acid substitution refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references that compile such methods, e.g., Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or Current Protocols in Molecular Biology, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made among amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D. Therefore, one can make conservative amino acid substitutions to the amino acid sequence of the proteins and polypeptides disclosed herein.

The isolated nucleic acids of the invention may be recombinant adeno-associated virus (AAV) vectors (rAAV vectors). In some embodiments, an isolated nucleic acid as described by the disclosure comprises a region (e.g., a first region) comprising a first adeno-associated virus (AAV) inverted terminal repeat (ITR), or a variant thereof. The isolated nucleic acid (e.g., the recombinant AAV vector) may be packaged into a capsid protein and administered to a subject and/or delivered to a selected target cell. “Recombinant AAV (rAAV) vectors” are typically composed of, at a minimum, a transgene and its regulatory sequences, and 5' and 3' AAV inverted terminal repeats (ITRs). The transgene may comprise, as disclosed elsewhere herein, one or more regions that encode one or more proteins (e.g., human CEP290, or a fragment thereof). The transgene may also comprise a region encoding, for example, a miRNA binding site, and/or an expression control sequence (e.g., a poly-A tail), as described elsewhere in the disclosure.

Generally, ITR sequences are about 145 bp in length. Preferably, substantially the entire sequences encoding the ITRs are used in the molecule, although some degree of minor modification of these sequences is permissible. The ability to modify these ITR sequences is within the skill of the art. (See, e.g., texts such as Sambrook et al., “Molecular Cloning. A Laboratory Manual”, 2d ed., Cold Spring Harbor Laboratory, New York (1989); and K. Fisher et al., J Virol., 70:520-532 (1996)). An example of such a molecule employed in the present invention is a “cis-acting” plasmid containing the transgene, in which the selected transgene sequence and associated regulatory elements are flanked by the 5' and 3' AAV ITR sequences. In some embodiments, one or more additional nucleotide sequences are found between the transgene and the 5' and/or 3' AAV ITR sequences. The AAV ITR sequences may be obtained from any known AAV, including presently identified mammalian AAV types. In some embodiments, the isolated nucleic acid (e.g., the rAAV

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vector) comprises at least one ITR having a serotype selected from AAV1, AAV2, AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAV10, AAV11, and variants thereof. In some embodiments, the isolated nucleic acid comprises a region (e.g., a first region) encoding an AAV2 ITR.

In some embodiments, the isolated nucleic acid further comprises a region (e.g., a second region, a third region, a fourth region, etc.) comprising a second AAV ITR. In some embodiments, the second AAV ITR has a serotype selected from AAV1, AAV2, AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAV10, AAV11, and variants thereof. In some embodiments, the second ITR is a mutant ITR that lacks a functional terminal resolution site (TRS). The term "lacking a terminal resolution site" can refer to an AAV ITR that comprises a mutation (e.g., a sense mutation such as a non-synonymous mutation, or missense mutation) that abrogates the function of the terminal resolution site (TRS) of the ITR, or to a truncated AAV ITR that lacks a nucleic acid sequence encoding a functional TRS (e.g., a ΔTRS ITR). Without wishing to be bound by any particular theory, a rAAV vector comprising an ITR lacking a functional TRS produces a self-complementary rAAV vector, for example as described by McCarthy (2008) *Molecular Therapy* 16(10): 1648-1656.

In addition to the major elements identified above for the recombinant AAV vector, the vector also includes conventional control elements which are operably linked with elements of the transgene in a manner that permits its transcription, translation and/or expression in a cell transfected with the vector or infected with the virus produced by the invention. As used herein, "operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in trans or at a distance to control the gene of interest. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences (e.g., Nrl-response element, CRX-response element, RET-1, etc.); efficient RNA processing signals such as splicing and polyadenylation (polyA) signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance secretion of the encoded product. A number of expression control sequences, including promoters which are native, constitutive, inducible and/or tissue-specific, are known in the art and may be utilized.

As used herein, a nucleic acid sequence (e.g., coding sequence) and regulatory sequences are said to be operably linked when they are covalently linked in such a way as to place the expression or transcription of the nucleic acid sequence under the influence or control of the regulatory sequences. If it is desired that the nucleic acid sequences be translated into a functional protein, two DNA sequences are said to be operably linked if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region would be operably linked to a nucleic acid sequence if the promoter region were capable of effecting transcription of that DNA sequence such that the resulting transcript might be translated into the desired protein or polypeptide. Similarly two or more coding regions are

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operably linked when they are linked in such a way that their transcription from a common promoter results in the expression of two or more proteins having been translated in frame. In some embodiments, operably linked coding sequences yield a fusion protein. In some embodiments, operably linked coding sequences yield a functional RNA (e.g., miRNA).

A "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene. The phrases "operatively positioned," "under control" or "under transcriptional control" means that the promoter is in the correct location and orientation in relation to the nucleic acid to control RNA polymerase initiation and expression of the gene.

For nucleic acids encoding proteins, a polyadenylation sequence generally is inserted following the transgene sequences and before the 3' AAV ITR sequence. A rAAV construct useful in the present disclosure may also contain an intron, desirably located between the promoter/enhancer sequence and the transgene. One possible intron sequence is derived from SV-40, and is referred to as the SV-40 T intron sequence. Another vector element that may be used is an internal ribosome entry site (IRES). An IRES sequence is used to produce more than one polypeptide from a single gene transcript. An IRES sequence would be used to produce a protein that contain more than one polypeptide chains. Selection of these and other common vector elements are conventional and many such sequences are available [see, e.g., Sambrook et al., and references cited therein at, for example, pages 3.18 3.26 and 16.17 16.27 and Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1989]. In some embodiments, a Foot and Mouth Disease Virus 2A sequence is included in polyprotein; this is a small peptide (approximately 18 amino acids in length) that has been shown to mediate the cleavage of polyproteins (Ryan, M D et al., *EMBO*, 1994; 4: 928-933; Mattion, N M et al., *J Virology*, November 1996; p. 8124-8127; Furler, S et al., *Gene Therapy*, 2001; 8: 864-873; and Halpin, C et al., *The Plant Journal*, 1999; 4: 453-459). The cleavage activity of the 2A sequence has previously been demonstrated in artificial systems including plasmids and gene therapy vectors (AAV and retroviruses) (Ryan, M D et al., *EMBO*, 1994; 4: 928-933; Mattion, N M et al., *J Virology*, November 1996; p. 8124-8127; Furler, S et al., *Gene Therapy*, 2001; 8: 864-873; and Halpin, C et al., *The Plant Journal*, 1999; 4: 453-459; de Felipe, P et al., *Gene Therapy*, 1999; 6: 198-208; de Felipe, Petal., *Human Gene Therapy*, 2000; 11: 1921-1931.; and Klump, H et al., *Gene Therapy*, 2001; 8: 811-817).

Examples of constitutive promoters include, without limitation, the retroviral Rous sarcoma virus (RSV) LTR promoter (optionally with the RSV enhancer), the cytomegalovirus (CMV) promoter (optionally with the CMV enhancer) [see, e.g., Boshart et al., *Cell*, 41:521-530 (1985)], the SV40 promoter, the dihydrofolate reductase promoter, the β-actin promoter, the phosphoglycerol kinase (PGK) promoter, and the EF1α promoter [Invitrogen]. In some embodiments, a promoter is a CB6 promoter. In some embodiments, a transgene comprises a CB6 promoter operably linked to the nucleic acid sequence set forth in any one of SEQ ID NOs: 5-7, 20-29, and 34-35. In some embodiments, a promoter is an enhanced chicken β-actin promoter. In some embodiments, a promoter is a U6 promoter. In some embodiments, a promoter is a chicken beta-actin (CBA) promoter. In some embodiments, a transgene comprises a CBA promoter operably linked to the nucleic acid sequence

set forth in any one of SEQ ID NOs: 5-7, 20-29, and 34-35. In some embodiments, a longer version of a CB promoter is used. In some embodiments, longer versions of the CB promoter enhance expression of a transgene.

Inducible promoters allow regulation of gene expression and can be regulated by exogenously supplied compounds, environmental factors such as temperature, or the presence of a specific physiological state, e.g., acute phase, a particular differentiation state of the cell, or in replicating cells only. Inducible promoters and inducible systems are available from a variety of commercial sources, including, without limitation, Invitrogen, Clontech and Ariad. Many other systems have been described and can be readily selected by one of skill in the art. Examples of inducible promoters regulated by exogenously supplied promoters include the zinc-inducible sheep metallothioneine (MT) promoter, the dexamethasone (Dex)-inducible mouse mammary tumor virus (MMTV) promoter, the T7 polymerase promoter system (WO 98/10088); the ecdysone insect promoter (No et al., Proc. Natl. Acad. Sci. USA, 93:3346-3351 (1996)), the tetracycline-repressible system (Gossen et al., Proc. Natl. Acad. Sci. USA, 89:5547-5551 (1992)), the tetracycline-inducible system (Gossen et al., Science, 268:1766-1769 (1995), see also Harvey et al., Curr. Opin. Chem. Biol., 2:512-518 (1998)), the RU486-inducible system (Wang et al., Nat. Biotech., 15:239-243 (1997) and Wang et al., Gene Ther., 4:432-441 (1997)) and the rapamycin-inducible system (Magari et al., J. Clin. Invest., 100:2865-2872 (1997)). Still other types of inducible promoters which may be useful in this context are those which are regulated by a specific physiological state, e.g., temperature, acute phase, a particular differentiation state of the cell, or in replicating cells only.

In another embodiment, the native promoter for the transgene will be used. The native promoter may be preferred when it is desired that expression of the transgene should mimic the native expression. The native promoter may be used when expression of the transgene must be regulated temporally or developmentally, or in a tissue-specific manner, or in response to specific transcriptional stimuli. In a further embodiment, other native expression control elements, such as enhancer elements, polyadenylation sites or Kozak consensus sequences may also be used to mimic the native expression.

In some embodiments, the regulatory sequences impart tissue-specific gene expression capabilities. In some cases, the tissue-specific regulatory sequences bind tissue-specific transcription factors that induce transcription in a tissue specific manner. Such tissue-specific regulatory sequences (e.g., promoters, enhancers, etc.) are well known in the art. In some embodiments, the tissue-specific promoter is an eye-specific promoter. Examples of eye-specific promoters include but are not limited to a retinoschisin promoter, K12 promoter, a rhodopsin promoter, a rod-specific promoter, a cone-specific promoter, a rhodopsin kinase promoter, a GRK1 promoter, an interphotoreceptor retinoid-binding protein proximal (IRBP) promoter, retinal pigmented epithelium-specific promoter (e.g., RPE65, Best1, etc.) and an opsin promoter (e.g., a red opsin promoter, a blue opsin promoter, etc.). In some embodiments, a transgene comprises an IRBP promoter operably linked to the nucleic acid sequence set forth in any one of SEQ ID NOs: 5-7, 20-29, and 34-35.

In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence set forth in SEQ ID NO: 29 or 34. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence

encoding the amino acids 1-200 and 580-1180 of human CEP290. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence encoding the amino acids 1-200 and 580-1180 of SEQ ID NO: 1. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence set forth in SEQ ID NO: 19.

In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence set forth in SEQ ID NO: 35. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence encoding the amino acids 1-380 and 580-1180 of human CEP290. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence encoding the amino acids 1-380 and 580-1180 of SEQ ID NO: 1. In some embodiments, a transgene comprises a rhodopsin kinase promoter operably linked to the nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 36.

Aspects of the disclosure relate to isolated nucleic acids comprising a transgene encoding one or more CEP290 fragments and a photoreceptor-specific promoter. A photoreceptor-specific promoter may target rod photoreceptor cells, cone photoreceptor cells, or rod and cone photoreceptor cells. In some embodiments, the photoreceptor-specific promoter is a GRK promoter (e.g., a GRK promoter). In some embodiments, a transgene comprises a GRK promoter operably linked to the nucleic acid sequence set forth in any one of SEQ ID NOs: 5-7, 20-29, and 34-35.

In some embodiments, a transgene further comprises one or more (e.g., 1, 2, 3, 4, 5, or more) introns. The length of an intron may vary. In some embodiments, an intron ranges from between about 100 nucleotides in length to about 1000 nucleotides in length (e.g., between 100 and 500, 250 and 700, 500 and 1000, etc.). In some embodiments, an intron comprises a chicken beta-actin (CBA) intron, for example as set forth in SEQ ID NO: 37. In some embodiments, an intron comprises a synthetic intron, for example an intron comprising the sequence set forth in SEQ ID NO: 38. In some embodiments, an intron comprises a MBL intron, for example as set forth in SEQ ID NO: 39. In some embodiments, an intron is positioned between a promoter (e.g., a CBA promoter, etc.) and a miniCEP290 protein coding sequence (e.g., a sequence set forth in any one of SEQ ID NOs: 5-7, 20-29, and 34-35).

In some aspects, the disclosure relates to an rAAV vector comprising an expression cassette comprising a nucleic acid encoding the sequence set forth in SEQ ID NO: 29 or 34 (e.g., a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 19) operably linked to a rhodopsin kinase (RK) promoter, wherein the expression cassette is flanked by AAV2 ITRs. In some embodiments, the rAAV vector is encapsidated by one or more AAV capsid proteins. In some embodiments, the one or more AAV capsid proteins are AAV8 capsid proteins or AAV5 capsid proteins.

In some embodiments, a promoter is a RNA polymerase III (pol III) promoter. Non-limiting examples of pol III promoters include U6 and H1 promoter sequences. In some embodiments, a promoter is a RNA polymerase II (pol II) promoter. Non-limiting examples of pol II promoters include T7, T3, SP6, RSV, and cytomegalovirus promoter sequences. In some embodiments, a pol III promoter sequence drives expression of one or more inhibitory nucleic acids and a pol II promoter sequence drives expression of a minigene.

Recombinant Adeno-Associated Viruses (rAAVs)

In some aspects, the disclosure provides isolated AAVs. As used herein with respect to AAVs, the term "isolated" refers to an AAV that has been artificially produced or obtained. Isolated AAVs may be produced using recombinant methods. Such AAVs are referred to herein as "recombinant AAVs". Recombinant AAVs (rAAVs) preferably have tissue-specific targeting capabilities, such that a nuclease and/or transgene of the rAAV will be delivered specifically to one or more predetermined tissue(s). The AAV capsid is an important element in determining these tissue-specific targeting capabilities. Thus, an rAAV having a capsid appropriate for the tissue being targeted can be selected.

In some aspects, the disclosure relates to an rAAV comprising (i) a nucleic acid (e.g., rAAV vector) comprising an expression cassette comprising a nucleic acid encoding the sequence set forth in SEQ ID NO: 29 or 34 (e.g., a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 19) operably linked to a rhodopsin kinase (RK) promoter, wherein the expression cassette is flanked by AAV2 ITRs, and (ii) one or more AAV capsid proteins. In some embodiments, the one or more capsid proteins are AAV5 or AAV8 capsid proteins.

Methods for obtaining recombinant AAVs having a desired capsid protein are well known in the art. (See, for example, US 2003/0138772), the contents of which are incorporated herein by reference in their entirety). Typically the methods involve culturing a host cell which contains a nucleic acid sequence encoding an AAV capsid protein; a functional rep gene; a recombinant AAV vector composed of, AAV inverted terminal repeats (ITRs) and a transgene; and sufficient helper functions to permit packaging of the recombinant AAV vector into the AAV capsid proteins. In some embodiments, capsid proteins are structural proteins encoded by the cap gene of an AAV. AAVs comprise three capsid proteins, virion proteins 1 to 3 (named VP1, VP2 and VP3), all of which are transcribed from a single cap gene via alternative splicing. In some embodiments, the molecular weights of VP1, VP2 and VP3 are respectively about 87 kDa, about 72 kDa and about 62 kDa. In some embodiments, upon translation, capsid proteins form a spherical 60-mer protein shell around the viral genome. In some embodiments, the functions of the capsid proteins are to protect the viral genome, deliver the genome and interact with the host. In some aspects, capsid proteins deliver the viral genome to a host in a tissue specific manner.

In some embodiments, an AAV capsid protein is of an AAV serotype selected from the group consisting of AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAV9, and AAV10. In some embodiments, an AAV capsid protein is of a serotype derived from a non-human primate, for example AAVrh8 serotype. In some embodiments, the AAV capsid protein is of a serotype that has tropism for the eye of a subject, for example an AAV (e.g., AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh.8, AAVrh.10, AAVrh.39 and AAVrh.43) that transduces ocular cells of a subject more efficiently than other vectors. In some embodiments, an AAV capsid protein is of an AAV8 serotype or an AAV5 serotype. In some embodiments, the AAV capsid protein comprises the sequence set forth in SEQ ID NO: 9.

The components to be cultured in the host cell to package a rAAV vector in an AAV capsid may be provided to the host cell in trans. Alternatively, any one or more of the required components (e.g., recombinant AAV vector, rep sequences, cap sequences, and/or helper functions) may be provided by a stable host cell which has been engineered to contain one or more of the required components using methods known

to those of skill in the art. Most suitably, such a stable host cell will contain the required component(s) under the control of an inducible promoter. However, the required component(s) may be under the control of a constitutive promoter. Examples of suitable inducible and constitutive promoters are provided herein, in the discussion of regulatory elements suitable for use with the transgene. In still another alternative, a selected stable host cell may contain selected component(s) under the control of a constitutive promoter and other selected component(s) under the control of one or more inducible promoters. For example, a stable host cell may be generated which is derived from 293 cells (which contain E1 helper functions under the control of a constitutive promoter), but which contain the rep and/or cap proteins under the control of inducible promoters. Still other stable host cells may be generated by one of skill in the art.

In some embodiments, the instant disclosure relates to a host cell containing a nucleic acid that comprises a coding sequence encoding a protein (e.g., a CEP290 protein fragment). In some embodiments, the instant disclosure relates to a composition comprising the host cell described above. In some embodiments, the composition comprising the host cell above further comprises a cryopreservative.

The recombinant AAV vector, rep sequences, cap sequences, and helper functions required for producing the rAAV of the disclosure may be delivered to the packaging host cell using any appropriate genetic element (vector). The selected genetic element may be delivered by any suitable method, including those described herein. The methods used to construct any embodiment of this disclosure are known to those with skill in nucleic acid manipulation and include genetic engineering, recombinant engineering, and synthetic techniques. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. Similarly, methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present disclosure. See, e.g., K. Fisher et al., J. Virol., 70:520-532 (1993) and U.S. Pat. No. 5,478,745.

In some embodiments, recombinant AAVs may be produced using the triple transfection method (described in detail in U.S. Pat. No. 6,001,650). Typically, the recombinant AAVs are produced by transfecting a host cell with an recombinant AAV vector (comprising a transgene) to be packaged into AAV particles, an AAV helper function vector, and an accessory function vector. An AAV helper function vector encodes the "AAV helper function" sequences (i.e., rep and cap), which function in trans for productive AAV replication and encapsidation. Preferably, the AAV helper function vector supports efficient AAV vector production without generating any detectable wild-type AAV virions (i.e., AAV virions containing functional rep and cap genes). Non-limiting examples of vectors suitable for use with the present disclosure include pHLP19, described in U.S. Pat. No. 6,001,650 and pRep6cap6 vector, described in U.S. Pat. No. 6,156,303, the entirety of both incorporated by reference herein. The accessory function vector encodes nucleotide sequences for non-AAV derived viral and/or cellular functions upon which AAV is dependent for replication (i.e., "accessory functions"). The accessory functions include those functions required for AAV replication, including, without limitation, those moieties involved in activation of AAV gene transcription, stage specific AAV mRNA splicing, AAV DNA replication, synthesis of cap expression products, and AAV capsid assembly. Viral-based accessory functions can be derived from any of the known helper viruses such as adenovirus, herpesvirus (other than herpes simplex virus type-1), and vaccinia virus.

In some aspects, the disclosure provides transfected host cells. The term "transfection" is used to refer to the uptake of foreign DNA by a cell, and a cell has been "transfected" when exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are generally known in the art. See, e.g., Graham et al. (1973) Virology, 52:456, Sambrook et al. (1989) Molecular Cloning, a laboratory manual, Cold Spring Harbor Laboratories, New York, Davis et al. (1986) Basic Methods in Molecular Biology, Elsevier, and Chu et al. (1981) Gene 13:197. Such techniques can be used to introduce one or more exogenous nucleic acids, such as a nucleotide integration vector and other nucleic acid molecules, into suitable host cells.

A "host cell" refers to any cell that harbors, or is capable of harboring, a substance of interest. Often a host cell is a mammalian cell. A host cell may be used as a recipient of an AAV helper construct, an AAV minigene plasmid, an accessory function vector, or other transfer DNA associated with the production of recombinant AAVs. The term includes the progeny of the original cell which has been transfected. Thus, a "host cell" as used herein may refer to a cell which has been transfected with an exogenous DNA sequence. It is understood that the progeny of a single parental cell may not necessarily be completely identical in morphology or in genomic or total DNA complement as the original parent, due to natural, accidental, or deliberate mutation.

As used herein, the term "cell line" refers to a population of cells capable of continuous or prolonged growth and division in vitro. Often, cell lines are clonal populations derived from a single progenitor cell. It is further known in the art that spontaneous or induced changes can occur in karyotype during storage or transfer of such clonal populations. Therefore, cells derived from the cell line referred to may not be precisely identical to the ancestral cells or cultures, and the cell line referred to includes such variants.

As used herein, the terms "recombinant cell" refers to a cell into which an exogenous DNA segment, such as DNA segment that leads to the transcription of a biologically-active polypeptide or production of a biologically active nucleic acid such as an RNA, has been introduced.

As used herein, the term "vector" includes any genetic element, such as a plasmid, phage, transposon, cosmid, chromosome, artificial chromosome, virus, virion, etc., which is capable of replication when associated with the proper control elements and which can transfer gene sequences between cells. Thus, the term includes cloning and expression vehicles, as well as viral vectors. In some embodiments, useful vectors are contemplated to be those vectors in which the nucleic acid segment to be transcribed is positioned under the transcriptional control of a promoter. The term "expression vector or construct" means any type of genetic construct containing a nucleic acid in which part or all of the nucleic acid encoding sequence is capable of being transcribed. In some embodiments, expression includes transcription of the nucleic acid, for example, to generate a biologically-active polypeptide product or functional RNA (e.g., guide RNA) from a transcribed gene.

The foregoing methods for packaging recombinant vectors in desired AAV capsids to produce the rAAVs of the disclosure are not meant to be limiting and other suitable methods will be apparent to the skilled artisan.

Delivery of CEP290 Transgenes to the Eye

Methods for delivering a transgene to ocular (e.g., photoreceptors, such as rod cells or cone cells, retinal cells, retinal pigmented epithelial cells, etc.) tissue in a subject are provided herein. The methods typically involve administering to a subject an effective amount of an isolated nucleic

acid, rAAV, or composition comprising a nucleic acid for expressing a transgene (e.g., a CEP290 protein fragment) in the subject. A subject may be any suitable mammalian organism. In some embodiments, a subject is a human. 5 Additional examples of subjects include mouse, rat, non-human primate, pig, dog, cat, or horse subjects.

An "effective amount" of a rAAV is an amount sufficient to infect a sufficient number of cells of a target tissue in a subject. In some embodiments, a target tissue is ocular (e.g., 10 photoreceptor, retinal, retinal pigmented epithelium, etc.) tissue. An effective amount may be an amount sufficient to have a therapeutic benefit in a subject, e.g., to improve in the subject one or more symptoms of disease, e.g., a symptom of an ocular ciliopathy (e.g., an ocular ciliopathy associated with a deletion or mutation of CEP290 gene, such as LCA). 15 In some cases, an effective amount may be an amount sufficient to produce a stable somatic transgenic animal model. The effective amount will depend on a variety of factors such as, for example, the species, age, weight, health 20 of the subject, and the ocular tissue to be targeted, and may thus vary among subject and tissue.

An effective amount may also depend on the rAAV used. The invention is based, in part on the recognition that rAAV comprising capsid proteins having a particular serotype (e.g., AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh.8, AAVrh.10, AAVrh.39, and AAVrh.43) mediate more efficient transduction of ocular (e.g., photoreceptor, retinal, etc.) tissue that rAAV comprising capsid proteins having a different serotype. Thus in some embodiments, the rAAV comprises a capsid protein of an AAV serotype selected from the group consisting of: AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh.8, AAVrh.10, AAVrh.39, and AAVrh.43. In some embodiments, the rAAV comprises a capsid protein of AAV8 serotype (SEQ ID NO: 9). In some embodiments, the capsid protein comprises an amino acid sequence that is at least 70%, at least 80%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 9. In some embodiments, the capsid protein is AAV5 capsid protein.

40 In certain embodiments, the effective amount of rAAV is 10^{10} , 10^{11} , 10^{12} , 10^{13} , or 10^{14} genome copies per kg. In certain embodiments, the effective amount of rAAV is 10^{10} , 10^{11} , 10^{12} , 10^{13} , 10^{14} , or 10^{15} genome copies per subject.

An effective amount may also depend on the mode of 45 administration. For example, targeting an ocular (e.g., photoreceptor, retinal, etc.) tissue by intrastromal administration or subcutaneous injection may require different (e.g., higher or lower) doses, in some cases, than targeting an ocular (e.g., photoreceptor, retinal, etc.) tissue by another method (e.g., systemic administration, topical administration, subretinal administration, etc.). In some embodiments, intrastromal injection (IS) of rAAV having certain serotypes (e.g., AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh.8, AAVrh.10, AAVrh.39, and AAVrh.43) mediates efficient transduction of 50 ocular (e.g., corneal, photoreceptor, retinal, etc.) cells. Thus, in some embodiments, the injection is intrastromal injection (IS). In some embodiments, the administration is via injection, optionally subretinal injection or intravitreal injection. In some embodiments, the injection is subretinal injection. 55 In some embodiments, the injection is superchoroidal injection. In some embodiments, the injection is topical administration (e.g., topical administration to an eye). In some cases, multiple doses of a rAAV are administered.

Without wishing to be bound by any particular theory, 60 efficient transduction of ocular (e.g., photoreceptor, retinal, retinal pigmented epithelial, etc.) cells by rAAV described herein may be useful for the treatment of a subject having an

ocular disease (e.g., an ocular ciliopathy). Accordingly, methods and compositions for treating ocular disease are also provided herein. In some aspects, the disclosure provides a method for treating an ocular ciliopathy (e.g., an ocular ciliopathy associated with a deletion or mutation of CEP290 gene), the method comprising: administering to a subject having or suspected of having an ocular ciliopathy an effective amount of rAAV, wherein the rAAV comprises (i) a capsid protein having a serotype selected from the group consisting of AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh.8, AAVrh.10, AAVrh.39, and AAVrh.43, and (ii) a nucleic acid comprising a promoter operably linked to a transgene (e.g., a transgene encoding a CEP290 protein fragment as described by the disclosure).

In some embodiments, administration of a rAAV (or isolated nucleic acid) as described by the disclosure results in transduction of a cell or cells comprising a cilium, optionally a photoreceptor sensory cilium. The photoreceptor (PR) sensory cilium is nucleated from the basal body at the apical surface of the inner segment. As the microtubules extend, they form a doublet microtubule structure, called the connecting cilium (CC). The CC is analogous to the transition zone of a prototypic cilium and extends into the outer segment (OS) of the photoreceptor cell. The CC acts as a conduit for unidirectional or bidirectional transport of cargo moieties between the inner and the outer segments. The CC also acts as a ‘gatekeeper’ to regulate the entry or exit of the cargo, which aids in the maintenance of its unique composition. In some embodiments, administration of a rAAV (or isolated nucleic acid) as described by the disclosure results in growth or formation of a photoreceptor sensory cilium, a connecting cilium, or a combination thereof.

In some embodiments, delivery of a rAAV (or isolated nucleic acid) as described by the disclosure, for example miniCEP290-1-200/580-1180, results in improved structural and/or functional rescue (e.g., as measured by ERG, immunofluorescence analysis, etc.) relative to previously described miniCEP290 vectors (e.g., miniCEP290-580-1180). In some embodiments, delivery of the rAAV improves structural and/or functional rescue by between 2-fold and 100-fold (e.g., 2, 3, 4, 5, 10, 20, 25, 50, 75, 100-fold). In some embodiments, delivery of the rAAV improves structural and/or functional rescue of more than 100-fold (e.g., 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, etc.).

The rAAVs may be delivered to a subject in compositions according to any appropriate methods known in the art. The rAAV, preferably suspended in a physiologically compatible carrier (i.e., in a composition), may be administered to a subject, i.e. host animal, such as a human, mouse, rat, cat, dog, sheep, rabbit, horse, cow, goat, pig, guinea pig, hamster, chicken, turkey, or a non-human primate (e.g., Macaque). In some embodiments, a host animal does not include a human.

Delivery of the rAAVs to a mammalian subject may be by, for example, intraocular injection, subretinal injection, superchoroidal injection, or topical administration (e.g., eye drops). In some embodiments, the intraocular injection is intrastromal injection, subconjunctival injection, or intravitreal injection. In some embodiments, the injection is not topical administration. Combinations of administration methods (e.g., topical administration and intrastromal injection) can also be used.

The compositions of the disclosure may comprise an rAAV alone, or in combination with one or more other viruses (e.g., a second rAAV encoding having one or more different transgenes, such as a plurality of rAAVs where each rAAV encodes a different CEP290 fragment). In some

embodiments, a composition comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more different rAAVs each having one or more different transgenes. The skilled artisan recognizes that in some embodiments, a subject is administered a plurality of isolated nucleic acids (or vectors, such as plasmids, lentiviral vectors, etc.), where each nucleic acid of the plurality encodes a different CEP290 fragment.

In some embodiments, a composition further comprises a pharmaceutically acceptable carrier. Suitable carriers may be readily selected by one of skill in the art in view of the indication for which the rAAV or composition is directed. For example, one suitable carrier includes saline, which may be formulated with a variety of buffering solutions (e.g., phosphate buffered saline). Other exemplary carriers include sterile saline, lactose, sucrose, calcium phosphate, gelatin, dextran, agar, pectin, peanut oil, sesame oil, and water. The selection of the carrier is not a limitation of the present disclosure.

Optionally, the compositions of the disclosure may contain, in addition to the rAAV and carrier(s), other pharmaceutical ingredients, such as preservatives, or chemical stabilizers. Suitable exemplary preservatives include chlorobutanol, potassium sorbate, sorbic acid, sulfur dioxide, propyl gallate, the parabens, ethyl vanillin, glycerin, phenol, and parachlorophenol. Suitable chemical stabilizers include gelatin and albumin.

The compositions (e.g., compositions comprising one or more rAAVs) are administered in sufficient amounts to transfect the cells of a desired tissue (e.g., ocular tissue, such as photoreceptor, retinal, etc., tissue) and to provide sufficient levels of gene transfer and expression without undue adverse effects. Examples of pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the selected organ (e.g., subretinal delivery to the eye), oral, inhalation (including intranasal and intratracheal delivery), intraocular, intravenous, intramuscular, subcutaneous, intradermal, intratumoral, and other parental routes of administration. Routes of administration may be combined, if desired.

The dose of rAAV virions required to achieve a particular “therapeutic effect,” e.g., the units of dose in genome copies/per kilogram of body weight (GC/kg), will vary based on several factors including, but not limited to: the route of rAAV virion administration, the level of gene or RNA expression required to achieve a therapeutic effect, the specific disease or disorder being treated, and the stability of the gene or RNA product. One of skill in the art can readily determine a rAAV virion dose range to treat a patient having a particular disease or disorder based on the aforementioned factors, as well as other factors.

An effective amount of an rAAV is an amount sufficient to target infect an animal, target a desired tissue. The effective amount will depend primarily on factors such as the species, age, weight, health of the subject, and the tissue to be targeted, and may thus vary among animal and tissue. In some embodiments, the volume of an rAAV (e.g., a composition comprising an rAAV) administered ranges from about 10 µl to about 1000 µl per eye. In some embodiments, an rAAV is administered at a dosage between about 10^{11} to about 10^{13} genome copies per eye, or from about 10^{11} to about 10^{14} rAAV genome copies/ml. In some embodiments, an effective amount is produced by multiple doses of an rAAV.

In some embodiments, a dose of rAAV is administered to a subject no more than once per calendar day (e.g., a 24-hour period). In some embodiments, the dose is administered to a subject only once in the lifetime of the subject. In some

embodiments, a single dose is administered in each eye of the subject only once in the lifetime of the subject. In some embodiments, administration is bilateral administration, and the doses may be administered about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, or about 2 months apart. In some embodiments, a dose of rAAV is administered to a subject no more than once per 2, 3, 4, 5, 6, or 7 calendar days. In some embodiments, a dose of rAAV is administered to a subject no more than once per calendar week (e.g., 7 calendar days). In some embodiments, a dose of rAAV is administered to a subject no more than bi-weekly (e.g., once in a two calendar week period). In some embodiments, a dose of rAAV is administered to a subject no more than once per calendar month (e.g., once in 30 calendar days). In some embodiments, a dose of rAAV is administered to a subject no more than once per six calendar months. In some embodiments, a dose of rAAV is administered to a subject no more than once per calendar year (e.g., 365 days or 366 days in a leap year). In some embodiments, a dose of rAAV is administered postnatally. In some embodiments, a dose of rAAV is administered postnatally between day 7 and day 13. In some embodiments, a dose of rAAV is administered postnatal day 10.

In some embodiments, rAAV compositions are formulated to reduce aggregation of AAV particles in the composition, particularly where high rAAV concentrations are present (e.g., $\sim 10^{13}$ GC/ml or more). Appropriate methods for reducing aggregation of may be used, including, for example, addition of surfactants, pH adjustment, salt concentration adjustment, etc. (See, e.g., Wright F R, et al., Molecular Therapy (2005) 12, 171-178, the contents of which are incorporated herein by reference.)

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens. Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 70% or 80% or more of the weight or volume of the total formulation. Naturally, the amount of active compound in each therapeutically-useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

In some embodiments, rAAVs in suitably formulated pharmaceutical compositions disclosed herein are delivered directly to target tissue, e.g., direct to ocular tissue (e.g., photoreceptor, retinal, etc., tissue). However, in certain circumstances it may be desirable to separately or in addition deliver the rAAV-based therapeutic constructs via another route, e.g., subcutaneously, intraparencreatically, intranasally, parenterally, intravenously, intramuscularly, intrathecally, or orally, intraperitoneally, or by inhalation. In some embodiments, the administration modalities as described in U.S. Pat. Nos. 5,543,158; 5,641,515 and 5,399,363 (each specifically incorporated herein by reference in its entirety) may be used to deliver rAAVs. In some embodiments, a preferred mode of administration is by intravitreal injection or subretinal injection.

The pharmaceutical forms suitable for injectable use include suspension-based formulations, sterile aqueous solutions or dispersions, and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. In many cases the form is sterile and fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For administration of an injectable aqueous solution, for example, the solution may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a suitable sterile aqueous medium may be employed. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the host. The person responsible for administration will, in any event, determine the appropriate dose for the individual host.

Sterile injectable solutions are prepared by incorporating the active rAAV in the required amount in the appropriate solvent with various of the other ingredients enumerated herein, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The rAAV compositions disclosed herein may also be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, cal-

cium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a host.

Delivery vehicles such as liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, may be used for the introduction of the compositions of the present disclosure into suitable host cells. In particular, the rAAV vector delivered transgenes may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically acceptable formulations of the nucleic acids or the rAAV constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art. Recently, liposomes were developed with improved serum stability and circulation half-times (U.S. Pat. No. 5,741,516). Further, various methods of liposome and liposome like preparations as potential drug carriers have been described (U.S. Pat. Nos. 5,567,434; 5,552,157; 5,565,213; 5,738,868 and 5,795,587).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures. In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs, radiotherapeutic agents, viruses, transcription factors and allosteric effectors into a variety of cultured cell lines and animals. In addition, several successful clinical trials examining the effectiveness of liposome-mediated drug delivery have been completed.

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)). MLVs generally have diameters of from 25 nm to 4 μm. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Alternatively, nanocapsule formulations of the rAAV may be used. Nanocapsules can generally entrap substances in a stable and reproducible way. To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded in vivo. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use.

Kits and Related Compositions

The agents described herein may, in some embodiments, be assembled into pharmaceutical or diagnostic or research kits to facilitate their use in therapeutic, diagnostic or research applications. A kit may include one or more con-

ainers housing the components of the disclosure and instructions for use. Specifically, such kits may include one or more agents described herein, along with instructions describing the intended application and the proper use of these agents. In certain embodiments agents in a kit may be in a pharmaceutical formulation and dosage suitable for a particular application and for a method of administration of the agents. Kits for research purposes may contain the components in appropriate concentrations or quantities for running various experiments.

In some embodiments, the instant disclosure relates to a kit for producing a rAAV, the kit comprising a container housing an isolated nucleic acid comprising a transgene encoding a CEP290 protein fragment having the amino acid sequence set forth in any one of SEQ ID NOs: 2-4 and 10-19. In some embodiments, the kit further comprises a container housing an isolated nucleic acid encoding an AAV capsid protein, for example an AAV8 capsid protein (e.g., SEQ ID NO: 9) or an AAV5 capsid protein.

The kit may be designed to facilitate use of the methods described herein by researchers and can take many forms. Each of the compositions of the kit, where applicable, may be provided in liquid form (e.g., in solution), or in solid form, (e.g., a dry powder). In certain cases, some of the compositions may be constitutable or otherwise processable (e.g., to an active form), for example, by the addition of a suitable solvent or other species (for example, water or a cell culture medium), which may or may not be provided with the kit. As used herein, "instructions" can define a component of instruction and/or promotion, and typically involve written instructions on or associated with packaging of the disclosure. Instructions also can include any oral or electronic instructions provided in any manner such that a user will clearly recognize that the instructions are to be associated with the kit, for example, audiovisual (e.g., videotape, DVD, etc.), Internet, and/or web-based communications, etc. The written instructions may be in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflect approval by the agency of manufacture, use or sale for animal administration.

The kit may contain any one or more of the components described herein in one or more containers. As an example, in one embodiment, the kit may include instructions for mixing one or more components of the kit and/or isolating and mixing a sample and applying to a subject. The kit may include a container housing agents described herein. The agents may be in the form of a liquid, gel or solid (powder). The agents may be prepared steriley, packaged in syringe and shipped refrigerated. Alternatively it may be housed in a vial or other container for storage. A second container may have other agents prepared steriley. Alternatively the kit may include the active agents premixed and shipped in a syringe, vial, tube, or other container.

Exemplary embodiments of the invention will be described in more detail by the following examples. These embodiments are exemplary of the invention, which one skilled in the art will recognize is not limited to the exemplary embodiments.

EXAMPLES

Example 1

65 Therapeutic Strategies for CEP290-LCA

The relative sparing of the central region of the CEP290-LCA patient retinas indicates that gene therapy may be a

viable option for visual restoration in patients. However, progress in the development of mutation-independent gene replacement strategies for CEP290-LCA has been delayed largely because of unsuitability of the long CEP290 gene to be packaged into conventional AAV vector system for gene therapy. This example describes delivery of CEP290 fragments via AAV to treat CEP290-LCA. In some embodiments, the described CEP290 fragments restore ciliary growth and photoreceptor function in a mutation-independent manner, and are thus useful for treatment of nonsyndromic LCA and retinal degeneration in systemic ciliopathies due to CEP290 mutations.

The full-length CEP290 cDNA is ~8 kb long, which generally exceeds the packaging limit of conventional AAV vectors. A schematic depiction of the full-length CEP290 gene representing the locations of distinct protein interaction domains is shown in FIG. 1. Here, CEP290 fragments that retain function in photoreceptors (PR) and can be delivered using the conventional AAV vectors were identified. As CEP290 is a ciliary protein and regulates cilia growth, an *in vitro* assay of cilia growth was developed in order to use as a surrogate marker to test the function of shorter CEP290 regions. It was observed that mouse embryonic fibroblasts (MEFs) derived from a Cep290-mutant ($Cep290^{rd16}$) mouse, which recapitulates the early onset severe PR degeneration phenotype, have fewer ciliated cells and the cells that formed cilia were shorter compared to controls. This observation is consistent with previous studies that revealed fewer and shorter cilia in fibroblasts derived from CEP290-LCA patient samples.

As shown in FIGS. 2A-2B, cilia of $Cep290^{rd16}$ MEFs are ~2.7 μ m in length as compared to controls, which have ~3.8 μ m long cilia. In addition, fewer cells with cilia were detected among $Cep290^{rd16}$ MEFs as compared to controls.

Next, the effect of expressing full-length human CEP290 protein on cilia length in $Cep290^{rd16}$ MEFs was investigated. It was observed that the full-length human CEP290 protein correctly localizes to cilia, as determined by co-staining with ARL13b, which is a cilia marker (FIG. 3). Expressing GFP protein did not result in its localization to cilia. Additionally, measurement of cilia length showed that expression of CEP290 protein significantly rescued the cilia length of $Cep290^{rd16}$ MEFs as compared to expression of GFP.

Construction of vCEP290

The CEP290 gene encodes a predominantly coiled-coil protein. Constructs that removed repetitive domains of human CEP290, such as plasmids encoding GFP-fused miniCEP290⁵⁸⁰⁻¹⁶⁹⁵, miniCEP290¹⁷⁵¹⁻²⁰⁵⁰ and miniCEP290²⁰³⁷⁻²⁴⁷⁹ (FIG. 4A), were produced. Variants were cloned into pEGFP-C1 vector expressing the gene under the control of CMV promoter. The constructs express stable CEP290 protein fragments as determined by immunoblot analysis of protein extracts from transiently transfected mouse embryonic fibroblasts (FIG. 4B; see arrows). To test the functional potential of the miniCEP290s, a surrogate assay system using $Cep290^{rd16}$ MEFs (mouse embryonic fibroblasts) was used. FIG. 9 shows additional examples of CEP290 variants.

Effect of vCEP290 on Cilia Length

As shown in FIG. 5A, expression of different GFP-vCEP290-encoding plasmids into $Cep290^{rd16}$ or wild type mouse embryonic fibroblasts indicates that vCEP290⁵⁸⁰⁻¹⁶⁹⁵ localizes predominantly to the basal bodies (co-localization with γ -tubulin) and proximal cilia (co-localization with ADP-Ribosylation Factor-Like 13B; ARL13B; ciliary marker). Expression of other variants indicated a relatively

diffuse pattern of localization. The ability of the vCEP290 to modulate cilia length in $Cep290^{rd16}$ fibroblasts was then assessed. As shown in FIG. 5B, cilia length of the mutant fibroblasts was significantly increased when vCEP290⁵⁸⁰⁻¹⁶⁹⁵ was expressed. Other variants, and the negative control expressing only GFP, did not reveal a change in the cilia length of the fibroblasts. No effect on cilia length of the wild type fibroblasts was observed.

Whether further shortening vCEP290⁵⁸⁰⁻¹⁶⁹⁵ will result in a cilia length rescue was then investigated. Plasmids encoding GFP-fused vCEP290⁵⁸⁰⁻¹¹⁸⁰ and vCEP290¹¹⁸¹⁻¹⁶⁹⁵ were produced and their expression, localization and potential to rescue cilia length in $Cep290^{rd16}$ fibroblasts were tested. Both variants exhibited optimal expression as determined by immunoblotting using anti-GFP antibody, and localization to cilia (FIGS. 6A-6B). Data for vCEP290¹¹⁸¹⁻¹⁶⁹⁵ indicate predominant localization to the base of cilia and diffuse staining around the basal body. Cilia rescue assay data indicate that expression of either variant results in a significant increase in the cilia length of $Cep290^{rd16}$ fibroblasts (FIG. 6C and FIG. 10).

Potential of vCEP290 *In Vivo*

Functionality of vCEP290 constructs *in vivo* was investigated. vCEP290⁵⁸⁰⁻¹¹⁸⁰, vCEP290¹¹⁸¹⁻¹⁶⁹⁵ and vCEP290²⁰³⁷⁻²⁴⁷⁹ (as negative control since it did not rescue the cilia length defect in the fibroblasts) were cloned into an AAV2 vector having a CBA promoter and containing an IRES (internal ribosome entry site) between the gene of interest (e.g., vCEP290) and GFP. This permits both CEP290 and GFP to be translated from a single bicistronic mRNA and assists in identifying transduced photoreceptors using an anti-GFP antibody. Each rAAV (e.g., AAV2/8-CBA-vCep290⁵⁸⁰⁻¹¹⁸⁰_IRES-GFP, AAV2/8-CBA-vCep290¹¹⁸¹⁻¹⁶⁹⁵_IRES-GFP, AAV2/8-CBA-vCep290²⁰³⁷⁻²⁴⁷⁹_IRES-GFP, and negative control AAV2/8-CBA-GFP) were injected at 8×10^9 vg/eye in 1 μ l volume into the subretinal space of $Cep290^{rd16}$ pups at P0 stage. The mice were assessed for PR function and retinal morphology up to 5 weeks after injection.

Analysis of PR function by electroretinography (ERG) at 3 weeks post-injection revealed improvement (25-30%) in both scotopic (rod PR-mediated) and photopic (cone PR-mediated) (FIGS. 7A-7B, and FIGS. 11-12) responses of the miniCEP290⁵⁸⁰⁻¹¹⁸⁰-injected mice. No improvement was detected using miniCEP290²⁰³⁷⁻²⁴⁷⁹ or GFP. Further analysis revealed that the improvement in the ERG was stable up to 4 weeks post injection.

The number of layers of the ONL, which correlates with PR survival, were also counted in retinal cryosections: ~6-7 layers were observed in $Cep290^{rd16}$ retinas injected with miniCep290⁵⁸⁰⁻¹¹⁸⁰; 4-5 layers were observed in $Cep290^{rd16}$ retinas injected with miniCep290¹¹⁸¹⁻¹⁶⁹⁵ and; 2-3 layers were observed in retinas injected with miniCep290²⁰³⁷⁻²⁴⁷⁹ or GFP (equivalent to uninjected $Cep290^{rd16}$ at 3 weeks of age), as shown in FIG. 8A. It was also observed that ultrathin sections of the $Cep290^{rd16}$ retinas injected with miniCEP290⁵⁸⁰⁻¹¹⁸⁰ exhibited significant preservation of the outer nuclear layer (ONL) (FIG. 8B).

The structural preservation of photoreceptor (PR) outer segment in the miniCEP290⁵⁸⁰⁻¹¹⁸⁰-injected mice was examined by staining with peripherin-RDS (retinal degeneration slow, PR outer segment marker 45). RDS is a structural protein that specifically localizes to the outer segment (OS) discs and maintains the OS structure. The miniCEP290⁵⁸⁰⁻¹¹⁸⁰-injected $Cep290^{rd16}$ mice exhibited improved RDS localization to the outer segment as compared to undetectable RDS expression in the GFP-injected

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mice (FIG. 8C). The expression of rhodopsin and cone opsins, two of the key phototransduction proteins, was also examined. Undetectable opsin expression was detected in the miniCEP290²⁰³⁷⁻²⁴⁷⁹-injected retinas. However, the miniCEP290⁵⁸⁰⁻¹¹⁸⁰-injected retinas revealed detectable expression of rhodopsin and cone opsins in the outer segments (FIG. 8D). Some staining of cone opsins in the inner segment and outer nuclear layer was also observed. Overall, the data indicate that the expression of miniCEP290⁵⁸⁰⁻¹¹⁸⁰ can improve the function, morphology and opsin trafficking of CEP290^{rd16} retinas.

Materials and Methods

Cell Culture, Transient Transfection and Immunostaining MEFs derived from the WT and Cep290^{rd16} mice were maintained in DMEM with 10% FBS. Transient transfection with GFP-CEP290-FL or GFP-miniCEP290s was performed using Lipofectamine 2000 (Thermo Fisher). The transfected cells were either harvested for immunoblotting or were serum-starved to induce cilia growth. The ciliated cells were then immunostained, imaged under Leica microscope (DM5500). Images were then processed for cilia length evaluation using Image J.

Constructs and AAV Production

For in vitro experiments, full-length or miniCEP290-expressing cDNAs were cloned into pEGFP-C1 plasmid expressing GFP-tagged proteins under the control of CMV promoter. For AAV production, the miniCEP290-encoding cDNAs were cloned into a pAAV2 vector plasmid between a CMVenhancer/CBA (chicken β-actin) promoter upstream of IRES (internal ribosome entry site) GFP and β-globin intron. This expression cassette was flanked with AAV2 inverted terminal repeats (ITRs). The recombinant AAV2 genomes were packaged with AAV8 capsid by HEK293-triple transfection method and purified by CsCl gradient centrifugation method.

Subretinal Injection

Wild type C57BL/6J mice were obtained from a commercial source. The Cep290^{rd16} mice were also obtained. The Cep290^{rd16} mouse pups (P0/P1) were subretinally injected unilaterally with 8×10^5 vg/μl (total volume 1 μl) of the virus.

ERG and Immunofluorescence Microscopy of the Retina

Scotopic and photopic ERGs were performed. For scotopic response, mice were dark adapted overnight and all procedures were performed under dim red light. Light adapted (photopic) ERGs were recorded after light adaptation with a background illumination of 30 cd/m² (white 6500 K) for 8 min.

Immunofluorescence microscopy was performed by staining retinal cryosection sections with primary antibodies: rhodopsin, M-opsin, and peripherin-RDS, ARL13B, GFP (Abcam), and γ-tubulin. After washing with PBS (phosphate buffered saline), Alexa-488 or Alexa-546-conjugated secondary antibodies were added and the sections were further incubated for 1 h. After washing, nuclei were stained with DAPI and cells were imaged using a Leica microscope (DM5500).

Example 2

This example describes *in vivo* experiments to investigate CEP290 minigene expression. Briefly, 10-day old rd16 mice were subretinally injected with a CEP290 minigene construct. Expression of the CEP290 minigene was driven by a GRK promoter. Post-injection, rod (scotopic) and cone (photopic) photoreceptor response was assessed. FIG. 13 shows scotopic a-wave and b-wave amplitude for 10-day old mice subretinally injected with the indicated miniCEP290

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construct (GRK-580-1180). ERG were recorded at the indicated days after injection. FIG. 14 shows photopic a-wave and b-wave amplitude for 10-day old mice subretinally injected with the indicated miniCEP290 construct (GRK-580-1180). ERG were recorded at the indicated days after injection. Data indicate a sustained response in rod cells of up to 67 days, and an increase in cone cell activity, relative to miniCEP290 constructs driven by a CB6 promoter.

In vitro experiments were also performed. FIG. 15 shows micrographs of rd16 mouse embryonic fibroblasts transiently transfected with cDNA encoding the indicated minigenes encoding the protein and GFP. Expression of the minigenes was driven by a CB6 promoter. FIG. 16 shows data for cilia length measurement of rd16 mouse embryonic fibroblasts transiently transfected with cDNA encoding the indicated minigenes encoding the protein and GFP. Data indicate an increase in cilia length in miniCEP290 transfected cells relative to control (GFP) transfected cells.

FIGS. 17A-17D show scotopic and photopic wave amplitudes of CB6-promoter driving the indicated minigenes were subretinally injected into 10 day old rd16 mice. FIG. 17A shows scotopic a-wave amplitude. FIG. 17B shows photopic b-wave amplitude. FIG. 17C shows scotopic b-wave amplitude. FIG. 17D shows ERG of rd16 mice injected with CB6-1-200-580-1180 miniCEP290. ERG were recorded at indicated days after injection and compared to others.

Example 3

FIG. 18 is a schematic depicting additional embodiments of CEP290 minigenes. In some embodiments, expression of the minigenes is driven by a CB6 promoter. In some embodiments, expression of the minigenes is driven by an eye-specific promoter, for example a Rhodopsin Kinase (RK) promoter such as a GRK promoter.

Mice at P10 stage were subretinally injected with the AAV-vectors encoding the minigene constructs. The minigene was encapsulated in an AAV8 capsid protein. The ERG was performed at the indicated ages after injection, as described in the Figures.

FIG. 19 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-580-1180 in subretinally-injected mice. Rescue effect lasted more than 10 weeks post-injection.

FIG. 20 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1181-2479 in subretinally-injected mice. Rescue effect lasted up to 8.5 weeks post-injection.

FIG. 21 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-580-1180/1800-2479 in subretinally-injected mice. Rescue effect lasted up to 5.5 weeks post-injection.

FIG. 22 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1181-1695/1966-2479 in subretinally-injected mice.

FIG. 23 shows representative data for ERG analysis of Rhodopsin Kinase (RK) promoter-driven expression of miniCEP290-1-200/580-1180 in subretinally-injected mice. Rescue effect lasted more than 14 weeks post-injection.

Example 4

Leber congenital amaurosis (LCA) is a debilitating eye disorder and is considered one of the most severe forms of retinal degeneration. Mutations in CEP290 (LCA10) account for >26% of all LCA cases and are the most frequent

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cause of LCA. Adeno-associated viral (AAV) vectors are currently the most efficient vectors for gene delivery to the retina. However, the development of a gene therapy for LCA10 has been challenging because the size of the CEP290 gene is too large to be packaged into conventional AAV vectors. Mutation specific anti-sense oligo and gene editing therapies have been previously reported.

This example describes a mutation-independent gene therapy delivered with an AAV vector to treat LCA10, that results in severe vision loss at infancy. Versions of CEP290 minigene constructs (miniCEP290) that are functional and can be delivered into the subretinal space using AAV vectors were produced.

CEP290 minigene [e.g., CEP290 amino acid 580-1180 domain] under the control of a ubiquitous promoter was observed to improve the function and survival of photoreceptors in neonatal Cep290-mutant mice (Cep290^{rd16}). However, the effect was short-lived with degeneration ensuing after 5 weeks of age. Data indicate that the expression of CEP290-580-1180 under the control of the photoreceptor-specific rhodopsin kinase promoter improved the electroretinogram (ERG) response for both rod and cone photoreceptors by ~1.5 folds. This example describes a miniCEP290 gene construct that encodes amino acids 1-200 and 580-1180 (miniCEP290-1-200/580-1180) which improved photoreceptor structural and functional rescue by ~500% when delivered at postnatal day 10 in Cep290^{rd16} mice. Data also indicate that the expression of the new miniCEP290 prolonged the survival and improved the protein trafficking defects in the photoreceptors in the Cep290^{rd16} mice.

FIGS. 24A-24C show a morphological analysis of Rhodopsin Kinase (RK) promoter driving miniCEP290-580-1180: the minigene was subretinally delivered with AAV8 at P10 stage. The analysis was performed at 9 weeks of age. FIG. 24A shows miniCEP290-580-1180 immunofluorescence analysis of the injected retinal region (GFP; longer arrows). FIG. 24B shows improvement in rhodopsin (longer arrows). Shorter arrows do not show GFP expression (non-transduced) and consequently exhibit undetectable rhodopsin expression. FIG. 24C shows nuclear staining also shows more nuclear layers in the outer nuclear layer (ONL) region in the transduced area (longer arrows and longer vertical bars) as compared to the untransduced region (shorter arrow and shorter vertical bar). Rescue effect lasted more than 14 weeks post-injection.

Example 5

Codon-optimized MiniCEP290 constructs were produced and packaged into rAAVs using AAV5 capsid proteins. The sequences were codon-optimized to increase protein production, reduce tandem rare codons (which can reduce the efficiency of translation or even disengage the translational machinery), prolong the half-life of the mRNA, and to break stem-loop structures. FIGS. 25A-25C show codon optimized miniCEP290 constructs. FIG. 25A shows codon optimized miniCEP290 1-200/580-1180 constructs with promoters (e.g., chicken beta-actin promoter) and different introns (chicken beta-actin intron, synthetic intron, MBL intron, etc.). FIG. 25B shows codon optimized miniCEP290 1-380/580-1180 constructs with different promoters and introns. FIG. 25C shows representative data for codon optimized miniCEP290 1-200/580-1180 constructs packaged into AAV5 capsid and injected subretinally into mice at

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P10 stage. The mice were then analyzed by ERG (both scotopic and photopic) at the ages indicated.

EQUIVALENTS

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, and/or methods, if such features, systems, articles, materials, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of."

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"Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other

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than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Use of ordinal terms such as "first," "second," "third," etc., in the claims to modify a claim element does not by itself connote any priority, precedence, or order of one claim element over another or the temporal order in which acts of a method are performed, but are used merely as labels to distinguish one claim element having a certain name from another element having a same name (but for use of the ordinal term) to distinguish the claim elements.

SEQUENCE LISTING

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41**42**

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 1070 1075 1080
 Arg Thr Ser Leu Lys Gln Met Glu Glu Arg Asn Phe Glu Leu Glu
 1085 1090 1095
 Thr Lys Phe Ala Glu Leu Thr Lys Ile Asn Leu Asp Ala Gln Lys
 1100 1105 1110
 Val Glu Gln Met Leu Arg Asp Glu Leu Ala Asp Ser Val Ser Lys
 1115 1120 1125
 Ala Val Ser Asp Ala Asp Arg Gln Arg Ile Leu Glu Leu Glu Lys
 1130 1135 1140
 Asn Glu Met Glu Leu Lys Val Glu Val Ser Lys Leu Arg Glu Ile
 1145 1150 1155
 Ser Asp Ile Ala Arg Arg Gln Val Glu Ile Leu Asn Ala Gln Gln
 1160 1165 1170
 Gln Ser Arg Asp Lys Glu Val Glu Ser Leu Arg Met Gln Leu Leu
 1175 1180 1185
 Asp Tyr Gln Ala Gln Ser Asp Glu Lys Ser Leu Ile Ala Lys Leu
 1190 1195 1200
 His Gln His Asn Val Ser Leu Gln Leu Ser Glu Ala Thr Ala Leu
 1205 1210 1215
 Gly Lys Leu Glu Ser Ile Thr Ser Lys Leu Gln Lys Met Glu Ala
 1220 1225 1230
 Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp Glu Lys Glu Gln Ala
 1235 1240 1245
 Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg Ala Lys His Leu
 1250 1255 1260
 Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser Gly Ala Leu
 1265 1270 1275
 Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile Gln Leu
 1280 1285 1290
 Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser Gln
 1295 1300 1305
 Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu
 1310 1315 1320
 Lys Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr
 1325 1330 1335
 Lys Gly Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu
 1340 1345 1350
 Leu Arg Leu Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp
 1355 1360 1365
 Lys Glu Glu Ile Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu
 1370 1375 1380
 Arg Thr Ile Ser Ser Leu Glu Glu Glu Ile Val Gln Gln Asn Lys
 1385 1390 1395
 Phe His Glu Glu Arg Gln Met Ala Trp Asp Gln Arg Glu Val Asp
 1400 1405 1410
 Leu Glu Arg Gln Leu Asp Ile Phe Asp Arg Gln Gln Asn Glu Ile
 1415 1420 1425
 Leu Asn Ala Ala Gln Lys Phe Glu Glu Ala Thr Gly Ser Ile Pro
 1430 1435 1440
 Asp Pro Ser Leu Pro Leu Pro Asn Gln Leu Glu Ile Ala Leu Arg
 1445 1450 1455

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Lys Ile Lys Glu Asn Ile Arg Ile Ile Leu Glu Thr Arg Ala Thr
1460 1465 1470

Cys Lys Ser Leu Glu Glu Lys Leu Lys Glu Lys Glu Ser Ala Leu
1475 1480 1485

Arg Leu Ala Glu Gln Asn Ile Leu Ser Arg Asp Lys Val Ile Asn
1490 1495 1500

Glu Leu Arg Leu Arg Leu Pro Ala Thr Ala Glu Arg Glu Lys Leu
1505 1510 1515

Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro Lys Ser His His
1520 1525 1530

Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg
1535 1540 1545

Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu
1550 1555 1560

Glu Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu
1565 1570 1575

Glu Asp Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp
1580 1585 1590

Ser Ser Leu Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys
1595 1600 1605

Gln Ser Pro Thr Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu
1610 1615 1620

Ala Glu Met Glu Gln Thr Val Ala Glu Gln Asp Asp Ser Leu Ser
1625 1630 1635

Ser Leu Leu Val Lys Leu Lys Lys Val Ser Gln Asp Leu Glu Arg
1640 1645 1650

Gln Arg Glu Ile Thr Glu Leu Lys Val Lys Glu Phe Glu Asn Ile
1655 1660 1665

Lys Leu Gln Leu Gln Glu Asn His Glu Asp Glu Val Lys Lys Val
1670 1675 1680

Lys Ala Glu Val Glu Asp Leu Lys Tyr Leu Leu Asp Gln Ser Gln
1685 1690 1695

Lys Glu Ser Gln Cys Leu Lys Ser Glu Leu Gln Ala Gln Lys Glu
1700 1705 1710

Ala Asn Ser Arg Ala Pro Thr Thr Thr Met Arg Asn Leu Val Glu
1715 1720 1725

Arg Leu Lys Ser Gln Leu Ala Leu Lys Glu Lys Gln Gln Lys Ala
1730 1735 1740

Leu Ser Arg Ala Leu Leu Glu Leu Arg Ala Glu Met Thr Ala Ala
1745 1750 1755

Ala Glu Glu Arg Ile Ile Ser Ala Thr Ser Gln Lys Glu Ala His
1760 1765 1770

Leu Asn Val Gln Gln Ile Val Asp Arg His Thr Arg Glu Leu Lys
1775 1780 1785

Thr Gln Val Glu Asp Leu Asn Glu Asn Leu Leu Lys Leu Lys Glu
1790 1795 1800

Ala Leu Lys Thr Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp Asn
1805 1810 1815

Leu Asn Asp Leu Asn Asn Glu Leu Gln Lys Gln Lys Ala Tyr
1820 1825 1830

Asn Lys Ile Leu Arg Glu Lys Glu Glu Ile Asp Gln Glu Asn Asp
1835 1840 1845

Glu Leu Lys Arg Gln Ile Lys Arg Leu Thr Ser Gly Leu Gln Gly

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1850	1855	1860
Lys Pro Leu Thr Asp Asn Lys Gln Ser Leu Ile Glu Glu Leu Gln		
1865	1870	1875
Arg Lys Val Lys Lys Leu Glu Asn Gln Leu Glu Gly Lys Val Glu		
1880	1885	1890
Glu Val Asp Leu Lys Pro Met Lys Glu Lys Asn Ala Lys Glu Glu		
1895	1900	1905
Leu Ile Arg Trp Glu Glu Gly Lys Lys Trp Gln Ala Lys Ile Glu		
1910	1915	1920
Gly Ile Arg Asn Lys Leu Lys Glu Lys Glu Gly Glu Val Phe Thr		
1925	1930	1935
Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp Leu Phe Ala Lys Ala		
1940	1945	1950
Asp Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu Lys Thr Thr Gly		
1955	1960	1965
Met Thr Val Asp Gln Val Leu Gly Ile Arg Ala Leu Glu Ser Glu		
1970	1975	1980
Lys Glu Leu Glu Glu Leu Lys Lys Arg Asn Leu Asp Leu Glu Asn		
1985	1990	1995
Asp Ile Leu Tyr Met Arg Ala His Gln Ala Leu Pro Arg Asp Ser		
2000	2005	2010
Val Val Glu Asp Leu His Leu Gln Asn Arg Tyr Leu Gln Glu Lys		
2015	2020	2025
Leu His Ala Leu Glu Lys Gln Phe Ser Lys Asp Thr Tyr Ser Lys		
2030	2035	2040
Pro Ser Ile Ser Gly Ile Glu Ser Asp Asp His Cys Gln Arg Glu		
2045	2050	2055
Gln Glu Leu Gln Lys Glu Asn Leu Lys Leu Ser Ser Glu Asn Ile		
2060	2065	2070
Glu Leu Lys Phe Gln Leu Glu Gln Ala Asn Lys Asp Leu Pro Arg		
2075	2080	2085
Leu Lys Asn Gln Val Arg Asp Leu Lys Glu Met Cys Glu Phe Leu		
2090	2095	2100
Lys Lys Glu Lys Ala Glu Val Gln Arg Lys Leu Gly His Val Arg		
2105	2110	2115
Gly Ser Gly Arg Ser Gly Lys Thr Ile Pro Glu Leu Glu Lys Thr		
2120	2125	2130
Ile Gly Leu Met Lys Lys Val Val Glu Lys Val Gln Arg Glu Asn		
2135	2140	2145
Glu Gln Leu Lys Lys Ala Ser Gly Ile Leu Thr Ser Glu Lys Met		
2150	2155	2160
Ala Asn Ile Glu Gln Glu Asn Glu Lys Leu Lys Ala Glu Leu Glu		
2165	2170	2175
Lys Leu Lys Ala His Leu Gly His Gln Leu Ser Met His Tyr Glu		
2180	2185	2190
Ser Lys Thr Lys Gly Thr Glu Lys Ile Ile Ala Glu Asn Glu Arg		
2195	2200	2205
Leu Arg Lys Glu Leu Lys Lys Glu Thr Asp Ala Ala Glu Lys Leu		
2210	2215	2220
Arg Ile Ala Lys Asn Asn Leu Glu Ile Leu Asn Glu Lys Met Thr		
2225	2230	2235
Val Gln Leu Glu Glu Thr Gly Lys Arg Leu Gln Phe Ala Glu Ser		
2240	2245	2250

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Arg Gly Pro Gln Leu Glu Gly Ala Asp Ser Lys Ser Trp Lys Ser
2255 2260 2265

Ile Val Val Thr Arg Met Tyr Glu Thr Lys Leu Lys Glu Leu Glu
2270 2275 2280

Thr Asp Ile Ala Lys Lys Asn Gln Ser Ile Thr Asp Leu Lys Gln
2285 2290 2295

Leu Val Lys Glu Ala Thr Glu Arg Glu Gln Lys Val Asn Lys Tyr
2300 2305 2310

Asn Glu Asp Leu Glu Gln Gln Ile Lys Ile Leu Lys His Val Pro
2315 2320 2325

Glu Gly Ala Glu Thr Glu Gln Gly Leu Lys Arg Glu Leu Gln Val
2330 2335 2340

Leu Arg Leu Ala Asn His Gln Leu Asp Lys Glu Lys Ala Glu Leu
2345 2350 2355

Ile His Gln Ile Glu Ala Asn Lys Asp Gln Ser Gly Ala Glu Ser
2360 2365 2370

Thr Ile Pro Asp Ala Asp Gln Leu Lys Glu Lys Ile Lys Asp Leu
2375 2380 2385

Glu Thr Gln Leu Lys Met Ser Asp Leu Glu Lys Gln His Leu Lys
2390 2395 2400

Glu Glu Ile Lys Lys Leu Lys Lys Glu Leu Glu Asn Phe Asp Pro
2405 2410 2415

Ser Phe Phe Glu Glu Ile Glu Asp Leu Lys Tyr Asn Tyr Lys Glu
2420 2425 2430

Glu Val Lys Lys Asn Ile Leu Leu Glu Glu Lys Val Lys Lys Leu
2435 2440 2445

Ser Glu Gln Leu Gly Val Glu Leu Thr Ser Pro Val Ala Ala Ser
2450 2455 2460

Glu Glu Phe Glu Asp Glu Glu Glu Ser Pro Val Asn Phe Pro Ile
2465 2470 2475

Tyr

<210> SEQ ID NO 2

<211> LENGTH: 1116

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg Lys Leu Asp
1 5 10 15

Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys Asn Glu Phe
20 25 30

Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu Arg Ser Arg
35 40 45

Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu Val Glu Glu
50 55 60

Asn Lys Gln Leu Glu Glu Gly Met Lys Glu Ile Leu Gln Ala Ile Lys
65 70 75 80

Glu Met Gln Lys Asp Pro Asp Val Lys Gly Gly Glu Thr Ser Leu Ile
85 90 95

Ile Pro Ser Leu Glu Arg Leu Val Asn Ala Ile Glu Ser Lys Asn Ala
100 105 110

Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln Val Asp Gln
115 120 125

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Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg Glu Ser Arg
 130 135 140
 Lys Glu Ala Ile Asn Tyr Ser Gln Gln Leu Ala Lys Ala Asn Leu Lys
 145 150 155 160
 Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln Ser Glu Gly
 165 170 175
 Ser Asn Val Val Phe Lys Gly Ile Asp Leu Pro Asp Gly Ile Ala Pro
 180 185 190
 Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu Ile His Leu
 195 200 205
 Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn Leu Glu Asp
 210 215 220
 Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg His Gln Gln
 225 230 235 240
 Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr Trp Lys Thr
 245 250 255
 Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu Asp Gln Val
 260 265 270
 Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu Leu Asn Ala
 275 280 285
 Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala Glu Asn Ser
 290 295 300
 Arg Lys Ile Thr Val Leu Gln Val Asn Glu Lys Ser Leu Ile Arg Gln
 305 310 315 320
 Tyr Thr Thr Leu Val Glu Leu Glu Arg Gln Leu Arg Lys Glu Asn Glu
 325 330 335
 Lys Gln Lys Asn Glu Leu Leu Ser Met Glu Ala Glu Val Cys Glu Lys
 340 345 350
 Ile Gly Cys Leu Gln Arg Phe Lys Glu Met Ala Ile Phe Lys Ile Ala
 355 360 365
 Ala Leu Gln Lys Val Val Asp Asn Ser Val Ser Leu Ser Glu Leu Glu
 370 375 380
 Leu Ala Asn Lys Gln Tyr Asn Glu Leu Thr Ala Lys Tyr Arg Asp Ile
 385 390 395 400
 Leu Gln Lys Asp Asn Met Leu Val Gln Arg Thr Ser Asn Leu Glu His
 405 410 415
 Leu Glu Cys Glu Asn Ile Ser Leu Lys Glu Gln Val Glu Ser Ile Asn
 420 425 430
 Lys Glu Leu Glu Ile Thr Lys Glu Lys Leu His Thr Ile Glu Gln Ala
 435 440 445
 Trp Glu Gln Glu Thr Lys Leu Gly Asn Glu Ser Ser Met Asp Lys Ala
 450 455 460
 Lys Lys Ser Ile Thr Asn Ser Asp Ile Val Ser Ile Ser Lys Lys Ile
 465 470 475 480
 Thr Met Leu Glu Met Lys Glu Leu Asn Glu Arg Gln Arg Ala Glu His
 485 490 495
 Cys Gln Lys Met Tyr Glu His Leu Arg Thr Ser Leu Lys Gln Met Glu
 500 505 510
 Glu Arg Asn Phe Glu Leu Glu Thr Lys Phe Ala Glu Leu Thr Lys Ile
 515 520 525
 Asn Leu Asp Ala Gln Lys Val Glu Gln Met Leu Arg Asp Glu Leu Ala
 530 535 540

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Asp Ser Val Ser Lys Ala Val Ser Asp Ala Asp Arg Gln Arg Ile Leu
 545 550 555 560
 Glu Leu Glu Lys Asn Glu Met Glu Leu Lys Val Glu Val Ser Lys Leu
 565 570 575
 Arg Glu Ile Ser Asp Ile Ala Arg Arg Gln Val Glu Ile Leu Asn Ala
 580 585 590
 Gln Gln Gln Ser Arg Asp Lys Glu Val Glu Ser Leu Arg Met Gln Leu
 595 600 605
 Leu Asp Tyr Gln Ala Gln Ser Asp Glu Lys Ser Leu Ile Ala Lys Leu
 610 615 620
 His Gln His Asn Val Ser Leu Gln Leu Ser Glu Ala Thr Ala Leu Gly
 625 630 635 640
 Lys Leu Glu Ser Ile Thr Ser Lys Leu Gln Lys Met Glu Ala Tyr Asn
 645 650 655
 Leu Arg Leu Glu Gln Lys Leu Asp Glu Lys Glu Gln Ala Leu Tyr Tyr
 660 665 670
 Ala Arg Leu Glu Gly Arg Asn Arg Ala Lys His Leu Arg Gln Thr Ile
 675 680 685
 Gln Ser Leu Arg Arg Gln Phe Ser Gly Ala Leu Pro Leu Ala Gln Gln
 690 695 700
 Glu Lys Phe Ser Lys Thr Met Ile Gln Leu Gln Asn Asp Lys Leu Lys
 705 710 715 720
 Ile Met Gln Glu Met Lys Asn Ser Gln Gln Glu His Arg Asn Met Glu
 725 730 735
 Asn Lys Thr Leu Glu Met Glu Leu Lys Leu Lys Gly Leu Glu Glu Leu
 740 745 750
 Ile Ser Thr Leu Lys Asp Thr Lys Gly Ala Gln Lys Val Ile Asn Trp
 755 760 765
 His Met Lys Ile Glu Glu Leu Arg Leu Gln Glu Leu Lys Leu Asn Arg
 770 775 780
 Glu Leu Val Lys Asp Lys Glu Glu Ile Lys Tyr Leu Asn Asn Ile Ile
 785 790 795 800
 Ser Glu Tyr Glu Arg Thr Ile Ser Ser Leu Glu Glu Ile Val Gln
 805 810 815
 Gln Asn Lys Phe His Glu Glu Arg Gln Met Ala Trp Asp Gln Arg Glu
 820 825 830
 Val Asp Leu Glu Arg Gln Leu Asp Ile Phe Asp Arg Gln Gln Asn Glu
 835 840 845
 Ile Leu Asn Ala Ala Gln Lys Phe Glu Glu Ala Thr Gly Ser Ile Pro
 850 855 860
 Asp Pro Ser Leu Pro Leu Pro Asn Gln Leu Glu Ile Ala Leu Arg Lys
 865 870 875 880
 Ile Lys Glu Asn Ile Arg Ile Ile Leu Glu Thr Arg Ala Thr Cys Lys
 885 890 895
 Ser Leu Glu Glu Lys Leu Lys Glu Lys Glu Ser Ala Leu Arg Leu Ala
 900 905 910
 Glu Gln Asn Ile Leu Ser Arg Asp Lys Val Ile Asn Glu Leu Arg Leu
 915 920 925
 Arg Leu Pro Ala Thr Ala Glu Arg Glu Lys Leu Ile Ala Glu Leu Gly
 930 935 940
 Arg Lys Glu Met Glu Pro Lys Ser His His Thr Leu Lys Ile Ala His
 945 950 955 960
 Gln Thr Ile Ala Asn Met Gln Ala Arg Leu Asn Gln Lys Glu Glu Val

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965	970	975
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Leu Lys Lys Tyr Gln Arg Leu Leu Glu Lys Ala Arg Glu Glu Gln Arg
 980 985 990
 Glu Ile Val Lys Lys His Glu Glu Asp Leu His Ile Leu His His Arg
 995 1000 1005
 Leu Glu Leu Gln Ala Asp Ser Ser Leu Asn Lys Phe Lys Gln Thr
 1010 1015 1020
 Ala Trp Asp Leu Met Lys Gln Ser Pro Thr Pro Val Pro Thr Asn
 1025 1030 1035
 Lys His Phe Ile Arg Leu Ala Glu Met Glu Gln Thr Val Ala Glu
 1040 1045 1050
 Gln Asp Asp Ser Leu Ser Ser Leu Leu Val Lys Leu Lys Lys Val
 1055 1060 1065
 Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile Thr Glu Leu Lys Val
 1070 1075 1080
 Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln Glu Asn His Glu
 1085 1090 1095
 Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp Leu Lys Tyr
 1100 1105 1110
 Leu Leu Asp
 1115

<210> SEQ ID NO 3

<211> LENGTH: 601

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg Lys Leu Asp
 1 5 10 15
 Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys Asn Glu Phe
 20 25 30
 Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu Arg Ser Arg
 35 40 45
 Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu Val Glu Glu
 50 55 60
 Asn Lys Gln Leu Glu Glu Gly Met Lys Glu Ile Leu Gln Ala Ile Lys
 65 70 75 80
 Glu Met Gln Lys Asp Pro Asp Val Lys Gly Gly Glu Thr Ser Leu Ile
 85 90 95
 Ile Pro Ser Leu Glu Arg Leu Val Asn Ala Ile Glu Ser Lys Asn Ala
 100 105 110
 Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln Val Asp Gln
 115 120 125
 Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg Glu Ser Arg
 130 135 140
 Lys Glu Ala Ile Asn Tyr Ser Gln Gln Leu Ala Lys Ala Asn Leu Lys
 145 150 155 160
 Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln Ser Glu Gly
 165 170 175
 Ser Asn Val Val Phe Lys Gly Ile Asp Leu Pro Asp Gly Ile Ala Pro
 180 185 190
 Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu Ile His Leu
 195 200 205

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Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn Leu Glu Asp
 210 215 220
 Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg His Gln Gln
 225 230 235 240
 Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr Trp Lys Thr
 245 250 255
 Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu Asp Gln Val
 260 265 270
 Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu Leu Asn Ala
 275 280 285
 Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala Glu Asn Ser
 290 295 300
 Arg Lys Ile Thr Val Leu Gln Val Asn Glu Lys Ser Leu Ile Arg Gln
 305 310 315 320
 Tyr Thr Thr Leu Val Glu Leu Glu Arg Gln Leu Arg Lys Glu Asn Glu
 325 330 335
 Lys Gln Lys Asn Glu Leu Leu Ser Met Glu Ala Glu Val Cys Glu Lys
 340 345 350
 Ile Gly Cys Leu Gln Arg Phe Lys Glu Met Ala Ile Phe Lys Ile Ala
 355 360 365
 Ala Leu Gln Lys Val Val Asp Asn Ser Val Ser Leu Ser Glu Leu Glu
 370 375 380
 Leu Ala Asn Lys Gln Tyr Asn Glu Leu Thr Ala Lys Tyr Arg Asp Ile
 385 390 395 400
 Leu Gln Lys Asp Asn Met Leu Val Gln Arg Thr Ser Asn Leu Glu His
 405 410 415
 Leu Glu Cys Glu Asn Ile Ser Leu Lys Glu Gln Val Glu Ser Ile Asn
 420 425 430
 Lys Glu Leu Glu Ile Thr Lys Glu Lys Leu His Thr Ile Glu Gln Ala
 435 440 445
 Trp Glu Gln Glu Thr Lys Leu Gly Asn Glu Ser Ser Met Asp Lys Ala
 450 455 460
 Lys Lys Ser Ile Thr Asn Ser Asp Ile Val Ser Ile Ser Lys Lys Ile
 465 470 475 480
 Thr Met Leu Glu Met Lys Glu Leu Asn Glu Arg Gln Arg Ala Glu His
 485 490 495
 Cys Gln Lys Met Tyr Glu His Leu Arg Thr Ser Leu Lys Gln Met Glu
 500 505 510
 Glu Arg Asn Phe Glu Leu Glu Thr Lys Phe Ala Glu Leu Thr Lys Ile
 515 520 525
 Asn Leu Asp Ala Gln Lys Val Glu Gln Met Leu Arg Asp Glu Leu Ala
 530 535 540
 Asp Ser Val Ser Lys Ala Val Ser Asp Ala Asp Arg Gln Arg Ile Leu
 545 550 555 560
 Glu Leu Glu Lys Asn Glu Met Glu Leu Lys Val Glu Val Ser Lys Leu
 565 570 575
 Arg Glu Ile Ser Asp Ile Ala Arg Arg Gln Val Glu Ile Leu Asn Ala
 580 585 590
 Gln Gln Gln Ser Arg Asp Lys Glu Val
 595 600

<210> SEQ ID NO 4

<211> LENGTH: 515

<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln Ser Asp Glu
 1 5 10 15

Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser Leu Gln Leu
 20 25 30

Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr Ser Lys Leu
 35 40 45

Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp Glu
 50 55 60

Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg Ala
 65 70 75 80

Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser Gly
 85 90 95

Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile Gln
 100 105 110

Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser Gln
 115 120 125

Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu Lys
 130 135 140

Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr Lys Gly
 145 150 155 160

Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu Leu Arg Leu
 165 170 175

Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys Glu Glu Ile
 180 185 190

Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr Ile Ser Ser
 195 200 205

Leu Glu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu Glu Arg Gln
 210 215 220

Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln Leu Asp Ile
 225 230 235 240

Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala Gln Lys Phe Glu
 245 250 255

Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu Pro Leu Pro Asn Gln
 260 265 270

Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu Asn Ile Arg Ile Ile Leu
 275 280 285

Glu Thr Arg Ala Thr Cys Lys Ser Leu Glu Glu Lys Leu Lys Glu Lys
 290 295 300

Glu Ser Ala Leu Arg Leu Ala Glu Gln Asn Ile Leu Ser Arg Asp Lys
 305 310 315 320

Val Ile Asn Glu Leu Arg Leu Arg Leu Pro Ala Thr Ala Glu Arg Glu
 325 330 335

Lys Leu Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro Lys Ser His
 340 345 350

His Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg
 355 360 365

Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu Glu
 370 375 380

Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu Glu Asp
 385 390 395 400

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Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp Ser Ser Leu
 405 410 415
 Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln Ser Pro Thr
 420 425 430
 Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu Met Glu Gln
 435 440 445
 Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu Val Lys Leu
 450 455 460
 Lys Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile Thr Glu Leu
 465 470 475 480
 Lys Val Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln Glu Asn His
 485 490 495
 Glu Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp Leu Lys Tyr
 500 505 510
 Leu Leu Asp
 515

<210> SEQ ID NO 5
 <211> LENGTH: 3606
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

actgaaaaca tttctcaagg agatagaata agtgaaagaa aattggattt attgagcctc 60
 aaaaatatga gtgaagcaca atcaaagaat gaatttctt caagagaact aattgaaaaa 120
 gaaaagagatt tagaaaggag taggacagtg atagccaaat ttcagaataa attaaaagaa 180
 ttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaag 240
 gaaaatgcaga aagatcctga tggtaaagga ggagaaacat ctctaattat ccctagcctt 300
 gaaagactag ttaatgctat agaatcaaag aatgcagaag gaatcttga tgcgagtcg 360
 catttgaag cccaaagtta tcagcttacc ggaagaaatg aagaattaag acaggagctc 420
 agggaatctc gggaaagggc tataaattat tcacagcagt tggcaaaagc taatttaag 480
 atagaccatc ttgaaaaaga aactagtctt ttacgacaat cagaaggatc gaatgttgc 540
 tttaaaggaa ttgacttacc tgatggata gcaccatcta gtgccagtat cattaattct 600
 cagaatgaat atttataaca tttgttacag gaactagaaa ataaagaaaa aaagttaag 660
 aattttagaag attcttttga agattacaac agaaaatttg ctgttaattcg tcatcaacaa 720
 agtttggtgt ataaagaata cctaaagtggaa aaggagacat ggaaaaacaga atctaaaaca 780
 ataaaagagg aaaagagaaa acttgaggat caagtccaaac aagatgctat aaaagtaaaa 840
 gaatataata atttgctcaa tgctttcag atggattcgg atgaaatgaa aaaaatactt 900
 gcagaaaata gtaggaaaat tactgttttga caagtgaatg aaaaatcact tataaggcaa 960
 tataacaacct tagttagaatt ggagcaca cttagaaaag aaaaatgagaa gcaaaagaat 1020
 gaatttggtgt caatggaggc tgaagtttgt gaaaaatttg ggtgttgca aagatttaag 1080
 gaaaatggcca ttttcaagat tgcaagcttc caaaaatggat tagataatag tgtttcttg 1140
 tctgaacttag aactggctaa taaacagttac aatgaactga ctgctaagta cagggacatc 1200
 ttgcaaaaag ataataatgct tggtcaaaga acaagtaact tggaacacct ggagtgtgaa 1260
 aacatctcct taaaagaaca agtggagtct ataaataaaag aactggagat tccaaggaa 1320
 aaacttcaca ctattgaaca agcctggaa cagggaaacta aattaggtaa tgaatctgc 1380
 atggataagg caaagaaaatc aataaccaac agtgacatttgc ttccatttc aaaaaaaaata 1440

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ctAGAAATTG	agaAGAATGA	aatGGAACTA	aaAGTTGAAG	tGTCAAACACT	gagAGAGATT	3540
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<212> TYPE: DNA

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<213> ORGANISM: Homo sapiens

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<213> ORGANISM: Homo sapiens

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atgcaagaaa	tgaaaaattc	tcaacaagaa	catagaaata	tggagaacaa	aacattggag	420
atggaattaa	aattaaaggg	ccttggaaagag	ttaataagca	ctttaaagga	taccaaagga	480
gcccaaagg	aatatcaactg	gcatacgaaa	atagaagaac	ttcgtttca	agaacttaaa	540
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gaatatgaac	gtacaatcag	cagtttggaa	gaagaaattt	tgcaacagaa	caagtttcat	660
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<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

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 <211> LENGTH: 738
 <212> TYPE: PRT
 <213> ORGANISM: Unknown
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Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Lys Pro
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Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
 35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80

Gln Gln Leu Gln Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140

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

Gly Lys Lys Gly Gln Gln Pro Ala Arg Lys Arg Leu Asn Phe Gly Gln
 165 170 175

Thr Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro
 180 185 190

Pro Ala Ala Pro Ser Gly Val Gly Pro Asn Thr Met Ala Ala Gly Gly
 195 200 205

Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser
 210 215 220

Ser Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val
 225 230 235 240

Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His
 245 250 255

Leu Tyr Lys Gln Ile Ser Asn Gly Thr Ser Gly Gly Ala Thr Asn Asp
 260 265 270

Asn Thr Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn
 275 280 285

Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn
 290 295 300

Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Ser Phe Lys Leu Phe Asn
 305 310 315 320

Ile Gln Val Lys Glu Val Thr Gln Asn Glu Gly Thr Lys Thr Ile Ala
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Asn Asn Leu Thr Ser Thr Ile Gln Val Phe Thr Asp Ser Glu Tyr Gln

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75

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Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Thr Tyr		
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Thr Phe Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser		
420	425	430
Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu		
435	440	445
Ser Arg Thr Gln Thr Thr Gly Gly Thr Ala Asn Thr Gln Thr Leu Gly		
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Phe Ser Gln Gly Pro Asn Thr Met Ala Asn Gln Ala Lys Asn Trp		
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Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Thr Thr Thr Gly		
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Gln Asn Asn Asn Ser Asn Phe Ala Trp Thr Ala Gly Thr Lys Tyr His		
500	505	510
Leu Asn Gly Arg Asn Ser Leu Ala Asn Pro Gly Ile Ala Met Ala Thr		
515	520	525
His Lys Asp Asp Glu Glu Arg Phe Phe Pro Ser Asn Gly Ile Leu Ile		
530	535	540
Phe Gly Lys Gln Asn Ala Ala Arg Asp Asn Ala Asp Tyr Ser Asp Val		
545	550	555
Met Leu Thr Ser Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr		
565	570	575
Glu Glu Tyr Gly Ile Val Ala Asp Asn Leu Gln Gln Asn Thr Ala		
580	585	590
Pro Gln Ile Gly Thr Val Asn Ser Gln Gly Ala Leu Pro Gly Met Val		
595	600	605
Trp Gln Asn Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile		
610	615	620
Pro His Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe		
625	630	635
Gly Leu Lys His Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val		
645	650	655
Pro Ala Asp Pro Pro Thr Thr Phe Asn Gln Ser Lys Leu Asn Ser Phe		
660	665	670
Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu		
675	680	685
Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr		
690	695	700
Ser Asn Tyr Tyr Lys Ser Thr Ser Val Asp Phe Ala Val Asn Thr Glu		
705	710	715
Gly Val Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg		
725	730	735
Asn Leu		

<210> SEQ ID NO 10
<211> LENGTH: 1299

-continued

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln Ser Asp Glu
 1 5 10 15

 Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser Leu Gln Leu
 20 25 30

 Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr Ser Lys Leu
 35 40 45

 Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp Glu
 50 55 60

 Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg Ala
 65 70 75 80

 Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser Gly
 85 90 95

 Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile Gln
 100 105 110

 Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser Gln
 115 120 125

 Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu Lys
 130 135 140

 Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr Lys Gly
 145 150 155 160

 Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu Leu Arg Leu
 165 170 175

 Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys Glu Glu Ile
 180 185 190

 Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr Ile Ser Ser
 195 200 205

 Leu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu Glu Arg Gln
 210 215 220

 Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln Leu Asp Ile
 225 230 235 240

 Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala Gln Lys Phe Glu
 245 250 255

 Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu Pro Leu Pro Asn Gln
 260 265 270

 Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu Asn Ile Arg Ile Ile Leu
 275 280 285

 Glu Thr Arg Ala Thr Cys Lys Ser Leu Glu Glu Lys Leu Lys Glu Lys
 290 295 300

 Glu Ser Ala Leu Arg Leu Ala Glu Gln Asn Ile Leu Ser Arg Asp Lys
 305 310 315 320

 Val Ile Asn Glu Leu Arg Leu Pro Ala Thr Ala Glu Arg Glu
 325 330 335

 Lys Leu Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro Lys Ser His
 340 345 350

 His Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg
 355 360 365

 Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu Glu
 370 375 380

 Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu Glu Asp
 385 390 395 400

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Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp Ser Ser Leu
 405 410 415
 Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln Ser Pro Thr
 420 425 430
 Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu Met Glu Gln
 435 440 445
 Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu Val Lys Leu
 450 455 460
 Lys Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile Thr Glu Leu
 465 470 475 480
 Lys Val Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln Glu Asn His
 485 490 495
 Glu Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp Leu Lys Tyr
 500 505 510
 Leu Leu Asp Gln Ser Gln Lys Glu Ser Gln Cys Leu Lys Ser Glu Leu
 515 520 525
 Gln Ala Gln Lys Glu Ala Asn Ser Arg Ala Pro Thr Thr Thr Met Arg
 530 535 540
 Asn Leu Val Glu Arg Leu Lys Ser Gln Leu Ala Leu Lys Glu Lys Gln
 545 550 555 560
 Gln Lys Ala Leu Ser Arg Ala Leu Leu Glu Leu Arg Ala Glu Met Thr
 565 570 575
 Ala Ala Ala Glu Glu Arg Ile Ile Ser Ala Thr Ser Gln Lys Glu Ala
 580 585 590
 His Leu Asn Val Gln Gln Ile Val Asp Arg His Thr Arg Glu Leu Lys
 595 600 605
 Thr Gln Val Glu Asp Leu Asn Glu Asn Leu Leu Lys Leu Lys Glu Ala
 610 615 620
 Leu Lys Thr Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp Asn Leu Asn
 625 630 635 640
 Asp Leu Asn Asn Glu Leu Gln Lys Gln Lys Ala Tyr Asn Lys Ile
 645 650 655
 Leu Arg Glu Lys Glu Glu Ile Asp Gln Glu Asn Asp Glu Leu Lys Arg
 660 665 670
 Gln Ile Lys Arg Leu Thr Ser Gly Leu Gln Gly Lys Pro Leu Thr Asp
 675 680 685
 Asn Lys Gln Ser Leu Ile Glu Glu Leu Gln Arg Lys Val Lys Lys Leu
 690 695 700
 Glu Asn Gln Leu Glu Gly Lys Val Glu Glu Val Asp Leu Lys Pro Met
 705 710 715 720
 Lys Glu Lys Asn Ala Lys Glu Glu Leu Ile Arg Trp Glu Glu Gly Lys
 725 730 735
 Lys Trp Gln Ala Lys Ile Glu Gly Ile Arg Asn Lys Leu Lys Glu Lys
 740 745 750
 Glu Gly Glu Val Phe Thr Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp
 755 760 765
 Leu Phe Ala Lys Ala Asp Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu
 770 775 780
 Lys Thr Thr Gly Met Thr Val Asp Gln Val Leu Gly Ile Arg Ala Leu
 785 790 795 800
 Glu Ser Glu Lys Glu Leu Glu Leu Lys Lys Arg Asn Leu Asp Leu
 805 810 815

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Glu Asn Asp Ile Leu Tyr Met Arg Ala His Gln Ala Leu Pro Arg Asp
 820 825 830
 Ser Val Val Glu Asp Leu His Leu Gln Asn Arg Tyr Leu Gln Glu Lys
 835 840 845
 Leu His Ala Leu Glu Lys Gln Phe Ser Lys Asp Thr Tyr Ser Lys Pro
 850 855 860
 Ser Ile Ser Gly Ile Glu Ser Asp Asp His Cys Gln Arg Glu Gln Glu
 865 870 875 880
 Leu Gln Lys Glu Asn Leu Lys Leu Ser Ser Glu Asn Ile Glu Leu Lys
 885 890 895
 Phe Gln Leu Glu Gln Ala Asn Lys Asp Leu Pro Arg Leu Lys Asn Gln
 900 905 910
 Val Arg Asp Leu Lys Glu Met Cys Glu Phe Leu Lys Lys Glu Lys Ala
 915 920 925
 Glu Val Gln Arg Lys Leu Gly His Val Arg Gly Ser Gly Arg Ser Gly
 930 935 940
 Lys Thr Ile Pro Glu Leu Glu Lys Thr Ile Gly Leu Met Lys Lys Val
 945 950 955 960
 Val Glu Lys Val Gln Arg Glu Asn Glu Gln Leu Lys Lys Ala Ser Gly
 965 970 975
 Ile Leu Thr Ser Glu Lys Met Ala Asn Ile Glu Gln Glu Asn Glu Lys
 980 985 990
 Leu Lys Ala Glu Leu Glu Lys Leu Lys Ala His Leu Gly His Gln Leu
 995 1000 1005
 Ser Met His Tyr Glu Ser Lys Thr Lys Gly Thr Glu Lys Ile Ile
 1010 1015 1020
 Ala Glu Asn Glu Arg Leu Arg Lys Glu Leu Lys Lys Glu Thr Asp
 1025 1030 1035
 Ala Ala Glu Lys Leu Arg Ile Ala Lys Asn Asn Leu Glu Ile Leu
 1040 1045 1050
 Asn Glu Lys Met Thr Val Gln Leu Glu Glu Thr Gly Lys Arg Leu
 1055 1060 1065
 Gln Phe Ala Glu Ser Arg Gly Pro Gln Leu Glu Gly Ala Asp Ser
 1070 1075 1080
 Lys Ser Trp Lys Ser Ile Val Val Thr Arg Met Tyr Glu Thr Lys
 1085 1090 1095
 Leu Lys Glu Leu Glu Thr Asp Ile Ala Lys Lys Asn Gln Ser Ile
 1100 1105 1110
 Thr Asp Leu Lys Gln Leu Val Lys Glu Ala Thr Glu Arg Glu Gln
 1115 1120 1125
 Lys Val Asn Lys Tyr Asn Glu Asp Leu Glu Gln Gln Ile Lys Ile
 1130 1135 1140
 Leu Lys His Val Pro Glu Gly Ala Glu Thr Glu Gln Gly Leu Lys
 1145 1150 1155
 Arg Glu Leu Gln Val Leu Arg Leu Ala Asn His Gln Leu Asp Lys
 1160 1165 1170
 Glu Lys Ala Glu Leu Ile His Gln Ile Glu Ala Asn Lys Asp Gln
 1175 1180 1185
 Ser Gly Ala Glu Ser Thr Ile Pro Asp Ala Asp Gln Leu Lys Glu
 1190 1195 1200
 Lys Ile Lys Asp Leu Glu Thr Gln Leu Lys Met Ser Asp Leu Glu
 1205 1210 1215
 Lys Gln His Leu Lys Glu Glu Ile Lys Lys Leu Lys Lys Glu Leu

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1220	1225	1230
Glu Asn Phe Asp Pro Ser Phe	Phe Glu Glu Ile Glu	Asp Leu Lys
1235	1240	1245
Tyr Asn Tyr Lys Glu Glu Val	Lys Lys Asn Ile Leu	Leu Glu Glu
1250	1255	1260
Lys Val Lys Lys Leu Ser Glu	Gln Leu Gly Val Glu	Leu Thr Ser
1265	1270	1275
Pro Val Ala Ala Ser Glu Glu	Phe Glu Asp Glu Glu	Glu Ser Pro
1280	1285	1290
Val Asn Phe Pro Ile Tyr		
1295		

<210> SEQ ID NO 11

<211> LENGTH: 400

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Ile	Leu	Thr	Lys	Glu	Ile	Asn	Lys	Leu	Glu	Leu	Lys	Ile	Ser	Asp	Phe
1				5			10				15				
Leu	Asp	Glu	Asn	Glu	Ala	Leu	Arg	Glu	Arg	Val	Gly	Leu	Glu	Pro	Lys
	20			25							30				
Thr	Met	Ile	Asp	Leu	Thr	Glu	Phe	Arg	Asn	Ser	Lys	His	Leu	Lys	Gln
	35			40							45				
Gln	Gln	Tyr	Arg	Ala	Glu	Asn	Gln	Ile	Leu	Leu	Lys	Glu	Ile	Glu	Ser
	50			55							60				
Leu	Glu	Glu	Glu	Arg	Leu	Asp	Leu	Lys	Lys	Ile	Arg	Gln	Met	Ala	
	65			70							75				80
Gln	Glu	Arg	Gly	Lys	Arg	Ser	Ala	Thr	Ser	Gly	Leu	Thr	Thr	Glu	Asp
	85			90							95				
Leu	Asn	Leu	Thr	Glu	Asn	Ile	Ser	Gln	Gly	Asp	Arg	Ile	Ser	Glu	Arg
	100			105							110				
Lys	Leu	Asp	Leu	Leu	Ser	Leu	Lys	Asn	Met	Ser	Glu	Ala	Gln	Ser	Lys
	115			120							125				
Asn	Glu	Phe	Leu	Ser	Arg	Glu	Ile	Glu	Lys	Glu	Arg	Asp	Leu	Glu	
	130			135							140				
Arg	Ser	Arg	Thr	Val	Ile	Ala	Lys	Phe	Gln	Asn	Lys	Leu	Lys	Glu	Leu
	145			150							155				160
Val	Glu	Glu	Asn	Lys	Gln	Leu	Glu	Gly	Met	Lys	Glu	Ile	Leu	Gln	
	165			170							175				
Ala	Ile	Lys	Glu	Met	Gln	Lys	Asp	Pro	Asp	Val	Lys	Gly	Glu	Thr	
	180			185							190				
Ser	Leu	Ile	Ile	Pro	Ser	Leu	Glu	Arg	Leu	Val	Asn	Ala	Ile	Glu	Ser
	195			200							205				
Lys	Asn	Ala	Glu	Gly	Ile	Phe	Asp	Ala	Ser	Leu	His	Leu	Lys	Ala	Gln
	210			215							220				
Val	Asp	Gln	Leu	Thr	Gly	Arg	Asn	Glu	Glu	Leu	Arg	Gln	Glu	Leu	Arg
	225			230							235				240
Glu	Ser	Arg	Lys	Glu	Ala	Ile	Asn	Tyr	Ser	Gln	Gln	Leu	Ala	Lys	Ala
	245			250							255				
Asn	Leu	Lys	Ile	Asp	His	Leu	Glu	Lys	Glu	Thr	Ser	Leu	Leu	Arg	Gln
	260			265							270				
Ser	Glu	Gly	Ser	Asn	Val	Val	Phe	Lys	Gly	Ile	Asp	Leu	Pro	Asp	Gly
	275			280							285				

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Ile Ala Pro Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu
290 295 300

Ile His Leu Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn
305 310 315 320

Leu Glu Asp Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg
325 330 335

His Gln Gln Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr
340 345 350

Trp Lys Thr Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu
355 360 365

Asp Gln Val Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu
370 375 380

Leu Asn Ala Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala
385 390 395 400

<210> SEQ ID NO 12

<211> LENGTH: 1029

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln Ser Asp Glu
1 5 10 15

Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser Leu Gln Leu
20 25 30

Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr Ser Lys Leu
35 40 45

Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp Glu
50 55 60

Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg Ala
65 70 75 80

Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser Gly
85 90 95

Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile Gln
100 105 110

Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser Gln
115 120 125

Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu Lys
130 135 140

Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr Lys Gly
145 150 155 160

Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu Leu Arg Leu
165 170 175

Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys Glu Glu Ile
180 185 190

Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr Ile Ser Ser
195 200 205

Leu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu Glu Arg Gln
210 215 220

Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln Leu Asp Ile
225 230 235 240

Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala Gln Lys Phe Glu
245 250 255

Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu Pro Leu Pro Asn Gln
260 265 270

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Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu Asn Ile Arg Ile Ile Leu
 275 280 285
 Glu Thr Arg Ala Thr Cys Lys Ser Leu Glu Glu Lys Leu Lys Glu Lys
 290 295 300
 Glu Ser Ala Leu Arg Leu Ala Glu Gln Asn Ile Leu Ser Arg Asp Lys
 305 310 315 320
 Val Ile Asn Glu Leu Arg Leu Arg Leu Pro Ala Thr Ala Glu Arg Glu
 325 330 335
 Lys Leu Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro Lys Ser His
 340 345 350
 His Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg
 355 360 365
 Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu Glu
 370 375 380
 Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu Glu Asp
 385 390 395 400
 Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp Ser Ser Leu
 405 410 415
 Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln Ser Pro Thr
 420 425 430
 Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu Met Glu Gln
 435 440 445
 Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu Val Lys Leu
 450 455 460
 Lys Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile Thr Glu Leu
 465 470 475 480
 Lys Val Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln Glu Asn His
 485 490 495
 Glu Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp Leu Lys Tyr
 500 505 510
 Leu Leu Asp Thr Thr Gly Met Thr Val Asp Gln Val Leu Gly Ile Arg
 515 520 525
 Ala Leu Glu Ser Glu Lys Glu Leu Glu Glu Leu Lys Lys Arg Asn Leu
 530 535 540
 Asp Leu Glu Asn Asp Ile Leu Tyr Met Arg Ala His Gln Ala Leu Pro
 545 550 555 560
 Arg Asp Ser Val Val Glu Asp Leu His Leu Gln Asn Arg Tyr Leu Gln
 565 570 575
 Glu Lys Leu His Ala Leu Glu Lys Gln Phe Ser Lys Asp Thr Tyr Ser
 580 585 590
 Lys Pro Ser Ile Ser Gly Ile Glu Ser Asp Asp His Cys Gln Arg Glu
 595 600 605
 Gln Glu Leu Gln Lys Glu Asn Leu Lys Leu Ser Ser Glu Asn Ile Glu
 610 615 620
 Leu Lys Phe Gln Leu Glu Gln Ala Asn Lys Asp Leu Pro Arg Leu Lys
 625 630 635 640
 Asn Gln Val Arg Asp Leu Lys Glu Met Cys Glu Phe Leu Lys Lys Glu
 645 650 655
 Lys Ala Glu Val Gln Arg Lys Leu Gly His Val Arg Gly Ser Gly Arg
 660 665 670
 Ser Gly Lys Thr Ile Pro Glu Leu Glu Lys Thr Ile Gly Leu Met Lys
 675 680 685

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Lys Val Val Glu Lys Val Gln Arg Glu Asn Glu Gln Leu Lys Lys Ala
690 695 700

Ser Gly Ile Leu Thr Ser Glu Lys Met Ala Asn Ile Glu Gln Glu Asn
705 710 715 720

Glu Lys Leu Lys Ala Glu Leu Glu Lys Leu Lys Ala His Leu Gly His
725 730 735

Gln Leu Ser Met His Tyr Glu Ser Lys Thr Lys Gly Thr Glu Lys Ile
740 745 750

Ile Ala Glu Asn Glu Arg Leu Arg Lys Glu Leu Lys Lys Glu Thr Asp
755 760 765

Ala Ala Glu Lys Leu Arg Ile Ala Lys Asn Asn Leu Glu Ile Leu Asn
770 775 780

Glu Lys Met Thr Val Gln Leu Glu Glu Thr Gly Lys Arg Leu Gln Phe
785 790 795 800

Ala Glu Ser Arg Gly Pro Gln Leu Glu Gly Ala Asp Ser Lys Ser Trp
805 810 815

Lys Ser Ile Val Val Thr Arg Met Tyr Glu Thr Lys Leu Lys Glu Leu
820 825 830

Glu Thr Asp Ile Ala Lys Lys Asn Gln Ser Ile Thr Asp Leu Lys Gln
835 840 845

Leu Val Lys Glu Ala Thr Glu Arg Glu Gln Lys Val Asn Lys Tyr Asn
850 855 860

Glu Asp Leu Glu Gln Gln Ile Lys Ile Leu Lys His Val Pro Glu Gly
865 870 875 880

Ala Glu Thr Glu Gln Gly Leu Lys Arg Glu Leu Gln Val Leu Arg Leu
885 890 895

Ala Asn His Gln Leu Asp Lys Glu Lys Ala Glu Leu Ile His Gln Ile
900 905 910

Glu Ala Asn Lys Asp Gln Ser Gly Ala Glu Ser Thr Ile Pro Asp Ala
915 920 925

Asp Gln Leu Lys Glu Lys Ile Lys Asp Leu Glu Thr Gln Leu Lys Met
930 935 940

Ser Asp Leu Glu Lys Gln His Leu Lys Glu Glu Ile Lys Lys Leu Lys
945 950 955 960

Lys Glu Leu Glu Asn Phe Asp Pro Ser Phe Phe Glu Glu Ile Glu Asp
965 970 975

Leu Lys Tyr Asn Tyr Lys Glu Glu Val Lys Lys Asn Ile Leu Leu Glu
980 985 990

Glu Lys Val Lys Lys Leu Ser Glu Gln Leu Gly Val Glu Leu Thr Ser
995 1000 1005

Pro Val Ala Ala Ser Glu Glu Phe Glu Asp Glu Glu Glu Ser Pro
1010 1015 1020

Val Asn Phe Pro Ile Tyr
1025

<210> SEQ ID NO 13
<211> LENGTH: 1281
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg Lys Leu Asp
1 5 10 15

Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys Asn Glu Phe
20 25 30

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Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu Arg Ser Arg
 35 40 45
 Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu Val Glu Glu
 50 55 60
 Asn Lys Gln Leu Glu Glu Gly Met Lys Glu Ile Leu Gln Ala Ile Lys
 65 70 75 80
 Glu Met Gln Lys Asp Pro Asp Val Lys Gly Gly Glu Thr Ser Leu Ile
 85 90 95
 Ile Pro Ser Leu Glu Arg Leu Val Asn Ala Ile Glu Ser Lys Asn Ala
 100 105 110
 Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln Val Asp Gln
 115 120 125
 Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg Glu Ser Arg
 130 135 140
 Lys Glu Ala Ile Asn Tyr Ser Gln Gln Leu Ala Lys Ala Asn Leu Lys
 145 150 155 160
 Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln Ser Glu Gly
 165 170 175
 Ser Asn Val Val Phe Lys Gly Ile Asp Leu Pro Asp Gly Ile Ala Pro
 180 185 190
 Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu Ile His Leu
 195 200 205
 Leu Gln Glu Leu Glu Asn Lys Glu Lys Leu Lys Asn Leu Glu Asp
 210 215 220
 Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg His Gln Gln
 225 230 235 240
 Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr Trp Lys Thr
 245 250 255
 Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu Asp Gln Val
 260 265 270
 Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu Leu Asn Ala
 275 280 285
 Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala Glu Asn Ser
 290 295 300
 Arg Lys Ile Thr Val Leu Gln Val Asn Glu Lys Ser Leu Ile Arg Gln
 305 310 315 320
 Tyr Thr Thr Leu Val Glu Leu Glu Arg Gln Leu Arg Lys Glu Asn Glu
 325 330 335
 Lys Gln Lys Asn Glu Leu Leu Ser Met Glu Ala Glu Val Cys Glu Lys
 340 345 350
 Ile Gly Cys Leu Gln Arg Phe Lys Glu Met Ala Ile Phe Lys Ile Ala
 355 360 365
 Ala Leu Gln Lys Val Val Asp Asn Ser Val Ser Leu Ser Glu Leu Glu
 370 375 380
 Leu Ala Asn Lys Gln Tyr Asn Glu Leu Thr Ala Lys Tyr Arg Asp Ile
 385 390 395 400
 Leu Gln Lys Asp Asn Met Leu Val Gln Arg Thr Ser Asn Leu Glu His
 405 410 415
 Leu Glu Cys Glu Asn Ile Ser Leu Lys Glu Gln Val Glu Ser Ile Asn
 420 425 430
 Lys Glu Leu Glu Ile Thr Lys Glu Lys Leu His Thr Ile Glu Gln Ala
 435 440 445

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Trp Glu Gln Glu Thr Lys Leu Gly Asn Glu Ser Ser Met Asp Lys Ala
 450 455 460
 Lys Lys Ser Ile Thr Asn Ser Asp Ile Val Ser Ile Ser Lys Lys Ile
 465 470 475 480
 Thr Met Leu Glu Met Lys Glu Leu Asn Glu Arg Gln Arg Ala Glu His
 485 490 495
 Cys Gln Lys Met Tyr Glu His Leu Arg Thr Ser Leu Lys Gln Met Glu
 500 505 510
 Glu Arg Asn Phe Glu Leu Glu Thr Lys Phe Ala Glu Leu Thr Lys Ile
 515 520 525
 Asn Leu Asp Ala Gln Lys Val Glu Gln Met Leu Arg Asp Glu Leu Ala
 530 535 540
 Asp Ser Val Ser Lys Ala Val Ser Asp Ala Asp Arg Gln Arg Ile Leu
 545 550 555 560
 Glu Leu Glu Lys Asn Glu Met Glu Leu Lys Val Glu Val Ser Lys Leu
 565 570 575
 Arg Glu Ile Ser Asp Ile Ala Arg Arg Gln Val Glu Ile Leu Asn Ala
 580 585 590
 Gln Gln Gln Ser Arg Asp Lys Glu Val Lys Leu Lys Glu Ala Leu Lys
 595 600 605
 Thr Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp Asn Leu Asn Asp Leu
 610 615 620
 Asn Asn Glu Leu Gln Lys Lys Gln Lys Ala Tyr Asn Lys Ile Leu Arg
 625 630 635 640
 Glu Lys Glu Glu Ile Asp Gln Glu Asn Asp Glu Leu Lys Arg Gln Ile
 645 650 655
 Lys Arg Leu Thr Ser Gly Leu Gln Gly Lys Pro Leu Thr Asp Asn Lys
 660 665 670
 Gln Ser Leu Ile Glu Glu Leu Gln Arg Lys Val Lys Lys Leu Glu Asn
 675 680 685
 Gln Leu Glu Gly Lys Val Glu Glu Val Asp Leu Lys Pro Met Lys Glu
 690 695 700
 Lys Asn Ala Lys Glu Glu Leu Ile Arg Trp Glu Glu Gly Lys Lys Trp
 705 710 715 720
 Gln Ala Lys Ile Glu Gly Ile Arg Asn Lys Leu Lys Glu Lys Glu Gly
 725 730 735
 Glu Val Phe Thr Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp Leu Phe
 740 745 750
 Ala Lys Ala Asp Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu Lys Thr
 755 760 765
 Thr Gly Met Thr Val Asp Gln Val Leu Gly Ile Arg Ala Leu Glu Ser
 770 775 780
 Glu Lys Glu Leu Glu Glu Leu Lys Lys Arg Asn Leu Asp Leu Glu Asn
 785 790 795 800
 Asp Ile Leu Tyr Met Arg Ala His Gln Ala Leu Pro Arg Asp Ser Val
 805 810 815
 Val Glu Asp Leu His Leu Gln Asn Arg Tyr Leu Gln Glu Lys Leu His
 820 825 830
 Ala Leu Glu Lys Gln Phe Ser Lys Asp Thr Tyr Ser Lys Pro Ser Ile
 835 840 845
 Ser Gly Ile Glu Ser Asp Asp His Cys Gln Arg Glu Gln Glu Leu Gln
 850 855 860
 Lys Glu Asn Leu Lys Leu Ser Ser Glu Asn Ile Glu Leu Lys Phe Gln

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865	870	875	880
Leu Glu Gln Ala Asn Lys Asp Leu Pro Arg Leu Lys Asn Gln Val Val Arg			
885	890	895	
Asp Leu Lys Glu Met Cys Glu Phe Leu Lys Lys Glu Lys Ala Glu Val			
900	905	910	
Gln Arg Lys Leu Gly His Val Arg Gly Ser Gly Arg Ser Gly Lys Thr			
915	920	925	
Ile Pro Glu Leu Glu Lys Thr Ile Gly Leu Met Lys Lys Val Val Glu			
930	935	940	
Lys Val Gln Arg Glu Asn Glu Gln Leu Lys Lys Ala Ser Gly Ile Leu			
945	950	955	960
Thr Ser Glu Lys Met Ala Asn Ile Glu Gln Glu Asn Glu Lys Leu Lys			
965	970	975	
Ala Glu Leu Glu Lys Leu Lys Ala His Leu Gly His Gln Leu Ser Met			
980	985	990	
His Tyr Glu Ser Lys Thr Lys Gly Thr Glu Lys Ile Ile Ala Glu Asn			
995	1000	1005	
Glu Arg Leu Arg Lys Glu Leu Lys Lys Glu Thr Asp Ala Ala Glu			
1010	1015	1020	
Lys Leu Arg Ile Ala Lys Asn Asn Leu Glu Ile Leu Asn Glu Lys			
1025	1030	1035	
Met Thr Val Gln Leu Glu Glu Thr Gly Lys Arg Leu Gln Phe Ala			
1040	1045	1050	
Glu Ser Arg Gly Pro Gln Leu Glu Gly Ala Asp Ser Lys Ser Trp			
1055	1060	1065	
Lys Ser Ile Val Val Thr Arg Met Tyr Glu Thr Lys Leu Lys Glu			
1070	1075	1080	
Leu Glu Thr Asp Ile Ala Lys Lys Asn Gln Ser Ile Thr Asp Leu			
1085	1090	1095	
Lys Gln Leu Val Lys Glu Ala Thr Glu Arg Glu Gln Lys Val Asn			
1100	1105	1110	
Lys Tyr Asn Glu Asp Leu Glu Gln Gln Ile Lys Ile Leu Lys His			
1115	1120	1125	
Val Pro Glu Gly Ala Glu Thr Glu Gln Gly Leu Lys Arg Glu Leu			
1130	1135	1140	
Gln Val Leu Arg Leu Ala Asn His Gln Leu Asp Lys Glu Lys Ala			
1145	1150	1155	
Glu Leu Ile His Gln Ile Glu Ala Asn Lys Asp Gln Ser Gly Ala			
1160	1165	1170	
Glu Ser Thr Ile Pro Asp Ala Asp Gln Leu Lys Glu Lys Ile Lys			
1175	1180	1185	
Asp Leu Glu Thr Gln Leu Lys Met Ser Asp Leu Glu Lys Gln His			
1190	1195	1200	
Leu Lys Glu Glu Ile Lys Lys Leu Lys Lys Glu Leu Glu Asn Phe			
1205	1210	1215	
Asp Pro Ser Phe Phe Glu Glu Ile Glu Asp Leu Lys Tyr Asn Tyr			
1220	1225	1230	
Lys Glu Glu Val Lys Lys Asn Ile Leu Leu Glu Glu Lys Val Lys			
1235	1240	1245	
Lys Leu Ser Glu Gln Leu Gly Val Glu Leu Thr Ser Pro Val Ala			
1250	1255	1260	
Ala Ser Glu Glu Phe Glu Asp Glu Glu Glu Ser Pro Val Asn Phe			
1265	1270	1275	

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Pro Ile Tyr
1280

<210> SEQ ID NO 14
<211> LENGTH: 786
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln Ser Asp Glu
1 5 10 15

Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser Leu Gln Leu
20 25 30

Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr Ser Lys Leu
35 40 45

Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp Glu
50 55 60

Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg Ala
65 70 75 80

Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser Gly
85 90 95

Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile Gln
100 105 110

Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser Gln
115 120 125

Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu Lys
130 135 140

Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr Lys Gly
145 150 155 160

Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu Leu Arg Leu
165 170 175

Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys Glu Glu Ile
180 185 190

Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr Ile Ser Ser
195 200 205

Leu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu Glu Arg Gln
210 215 220

Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln Leu Asp Ile
225 230 235 240

Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala Gln Lys Phe Glu
245 250 255

Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu Pro Leu Pro Asn Gln
260 265 270

Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu Asn Ile Arg Ile Ile Leu
275 280 285

Glu Thr Arg Ala Thr Cys Lys Ser Leu Glu Glu Lys Leu Lys Glu Lys
290 295 300

Glu Ser Ala Leu Arg Leu Ala Glu Gln Asn Ile Leu Ser Arg Asp Lys
305 310 315 320

Val Ile Asn Glu Leu Arg Leu Arg Leu Pro Ala Thr Ala Glu Arg Glu
325 330 335

Lys Leu Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro Lys Ser His
340 345 350

His Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg

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99**100**

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355	360	365
Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu Glu		
370	375	380
Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu Glu Asp		
385	390	395
Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp Ser Ser Leu		
405	410	415
Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln Ser Pro Thr		
420	425	430
Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu Met Glu Gln		
435	440	445
Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu Val Lys Leu		
450	455	460
Lys Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile Thr Glu Leu		
465	470	475
Lys Val Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln Glu Asn His		
485	490	495
Glu Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp Leu Lys Tyr		
500	505	510
Leu Leu Asp Gln Ser Gln Lys Glu Ser Gln Cys Leu Lys Ser Glu Leu		
515	520	525
Gln Ala Gln Lys Glu Ala Asn Ser Arg Ala Pro Thr Thr Thr Met Arg		
530	535	540
Asn Leu Val Glu Arg Leu Lys Ser Gln Leu Ala Leu Lys Glu Lys Gln		
545	550	555
Gln Lys Ala Leu Ser Arg Ala Leu Leu Glu Leu Arg Ala Glu Met Thr		
565	570	575
Ala Ala Ala Glu Glu Arg Ile Ile Ser Ala Thr Ser Gln Lys Glu Ala		
580	585	590
His Leu Asn Val Gln Gln Ile Val Asp Arg His Thr Arg Glu Leu Lys		
595	600	605
Thr Gln Val Glu Asp Leu Asn Glu Asn Leu Leu Lys Leu Lys Glu Ala		
610	615	620
Leu Lys Thr Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp Asn Leu Asn		
625	630	635
Asp Leu Asn Asn Glu Leu Gln Lys Lys Gln Lys Ala Tyr Asn Lys Ile		
645	650	655
Leu Arg Glu Lys Glu Glu Ile Asp Gln Glu Asn Asp Glu Leu Lys Arg		
660	665	670
Gln Ile Lys Arg Leu Thr Ser Gly Leu Gln Gly Lys Pro Leu Thr Asp		
675	680	685
Asn Lys Gln Ser Leu Ile Glu Glu Leu Gln Arg Lys Val Lys Lys Leu		
690	695	700
Glu Asn Gln Leu Glu Gly Lys Val Glu Glu Val Asp Leu Lys Pro Met		
705	710	715
Lys Glu Lys Asn Ala Lys Glu Glu Leu Ile Arg Trp Glu Glu Gly Lys		
725	730	735
Lys Trp Gln Ala Lys Ile Glu Gly Ile Arg Asn Lys Leu Lys Glu Lys		
740	745	750
Glu Gly Glu Val Phe Thr Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp		
755	760	765
Leu Phe Ala Lys Ala Asp Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu		
770	775	780

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Lys Thr
785

<210> SEQ ID NO 15
<211> LENGTH: 914
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Ile Leu Thr Lys Glu Ile Asn Lys Leu Glu Leu Lys Ile Ser Asp Phe
1 5 10 15

Leu Asp Glu Asn Glu Ala Leu Arg Glu Arg Val Gly Leu Glu Pro Lys
20 25 30

Thr Met Ile Asp Leu Thr Glu Phe Arg Asn Ser Lys His Leu Lys Gln
35 40 45

Gln Gln Tyr Arg Ala Glu Asn Gln Ile Leu Leu Lys Glu Ile Glu Ser
50 55 60

Leu Glu Glu Glu Arg Leu Asp Leu Lys Lys Ile Arg Gln Met Ala
65 70 75 80

Gln Glu Arg Gly Lys Arg Ser Ala Thr Ser Gly Leu Thr Thr Glu Asp
85 90 95

Leu Asn Leu Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg
100 105 110

Lys Leu Asp Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys
115 120 125

Asn Glu Phe Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu
130 135 140

Arg Ser Arg Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu
145 150 155 160

Val Glu Glu Asn Lys Gln Leu Glu Gly Met Lys Glu Ile Leu Gln
165 170 175

Ala Ile Lys Glu Met Gln Lys Asp Pro Asp Val Lys Gly Glu Thr
180 185 190

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

Lys Asn Ala Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln
210 215 220

Val Asp Gln Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg
225 230 235 240

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

Asn Leu Lys Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln
260 265 270

Ser Glu Gly Ser Asn Val Val Phe Lys Gly Ile Asp Leu Pro Asp Gly
275 280 285

Ile Ala Pro Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu
290 295 300

Ile His Leu Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn
305 310 315 320

Leu Glu Asp Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg
325 330 335

His Gln Gln Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr
340 345 350

Trp Lys Thr Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu

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103**104**

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355	360	365
Asp Gln Val Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu		
370	375	380
Leu Asn Ala Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala		
385	390	395
Thr Thr Gly Met Thr Val Asp Gln Val Leu Gly Ile Arg Ala Leu Glu		
405	410	415
Ser Glu Lys Glu Leu Glu Leu Lys Lys Arg Asn Leu Asp Leu Glu		
420	425	430
Asn Asp Ile Leu Tyr Met Arg Ala His Gln Ala Leu Pro Arg Asp Ser		
435	440	445
Val Val Glu Asp Leu His Leu Gln Asn Arg Tyr Leu Gln Glu Lys Leu		
450	455	460
His Ala Leu Glu Lys Gln Phe Ser Lys Asp Thr Tyr Ser Lys Pro Ser		
465	470	475
Ile Ser Gly Ile Glu Ser Asp Asp His Cys Gln Arg Glu Gln Glu Leu		
485	490	495
Gln Lys Glu Asn Leu Lys Leu Ser Ser Glu Asn Ile Glu Leu Lys Phe		
500	505	510
Gln Leu Glu Gln Ala Asn Lys Asp Leu Pro Arg Leu Lys Asn Gln Val		
515	520	525
Arg Asp Leu Lys Glu Met Cys Glu Phe Leu Lys Lys Glu Lys Ala Glu		
530	535	540
Val Gln Arg Lys Leu Gly His Val Arg Gly Ser Gly Arg Ser Gly Lys		
545	550	555
Thr Ile Pro Glu Leu Glu Lys Thr Ile Gly Leu Met Lys Lys Val Val		
565	570	575
Glu Lys Val Gln Arg Glu Asn Glu Gln Leu Lys Lys Ala Ser Gly Ile		
580	585	590
Leu Thr Ser Glu Lys Met Ala Asn Ile Glu Gln Glu Asn Glu Lys Leu		
595	600	605
Lys Ala Glu Leu Glu Lys Leu Lys Ala His Leu Gly His Gln Leu Ser		
610	615	620
Met His Tyr Glu Ser Lys Thr Lys Gly Thr Glu Lys Ile Ile Ala Glu		
625	630	635
Asn Glu Arg Leu Arg Lys Glu Leu Lys Lys Glu Thr Asp Ala Ala Glu		
645	650	655
Lys Leu Arg Ile Ala Lys Asn Asn Leu Glu Ile Leu Asn Glu Lys Met		
660	665	670
Thr Val Gln Leu Glu Glu Thr Gly Lys Arg Leu Gln Phe Ala Glu Ser		
675	680	685
Arg Gly Pro Gln Leu Glu Gly Ala Asp Ser Lys Ser Trp Lys Ser Ile		
690	695	700
Val Val Thr Arg Met Tyr Glu Thr Lys Leu Lys Glu Leu Glu Thr Asp		
705	710	715
Ile Ala Lys Lys Asn Gln Ser Ile Thr Asp Leu Lys Gln Leu Val Lys		
725	730	735
Glu Ala Thr Glu Arg Glu Gln Lys Val Asn Lys Tyr Asn Glu Asp Leu		
740	745	750
Glu Gln Gln Ile Lys Ile Leu Lys His Val Pro Glu Gly Ala Glu Thr		
755	760	765
Glu Gln Gly Leu Lys Arg Glu Leu Gln Val Leu Arg Leu Ala Asn His		
770	775	780

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105**106**

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Gln Leu Asp Lys Glu Lys Ala Glu Leu Ile His Gln Ile Glu Ala Asn
 785 790 795 800
 Lys Asp Gln Ser Gly Ala Glu Ser Thr Ile Pro Asp Ala Asp Gln Leu
 805 810 815
 Lys Glu Lys Ile Lys Asp Leu Glu Thr Gln Leu Lys Met Ser Asp Leu
 820 825 830
 Glu Lys Gln His Leu Lys Glu Glu Ile Lys Lys Leu Lys Lys Glu Leu
 835 840 845
 Glu Asn Phe Asp Pro Ser Phe Phe Glu Glu Ile Glu Asp Leu Lys Tyr
 850 855 860
 Asn Tyr Lys Glu Glu Val Lys Lys Asn Ile Leu Leu Glu Glu Lys Val
 865 870 875 880
 Lys Lys Leu Ser Glu Gln Leu Gly Val Glu Leu Thr Ser Pro Val Ala
 885 890 895
 Ala Ser Glu Glu Phe Glu Asp Glu Glu Glu Ser Pro Val Asn Phe Pro
 900 905 910
 Ile Tyr

<210> SEQ ID NO 16
<211> LENGTH: 885
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 16

Ile Leu Thr Lys Glu Ile Asn Lys Leu Glu Leu Lys Ile Ser Asp Phe
 1 5 10 15
 Leu Asp Glu Asn Glu Ala Leu Arg Glu Arg Val Gly Leu Glu Pro Lys
 20 25 30
 Thr Met Ile Asp Leu Thr Glu Phe Arg Asn Ser Lys His Leu Lys Gln
 35 40 45
 Gln Gln Tyr Arg Ala Glu Asn Gln Ile Leu Leu Lys Glu Ile Glu Ser
 50 55 60
 Leu Glu Glu Glu Arg Leu Asp Leu Lys Lys Ile Arg Gln Met Ala
 65 70 75 80
 Gln Glu Arg Gly Lys Arg Ser Ala Thr Ser Gly Leu Thr Thr Glu Asp
 85 90 95
 Leu Asn Leu Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln
 100 105 110
 Ser Asp Glu Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser
 115 120 125
 Leu Gln Leu Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr
 130 135 140
 Ser Lys Leu Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys
 145 150 155 160
 Leu Asp Glu Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg
 165 170 175
 Asn Arg Ala Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln
 180 185 190
 Phe Ser Gly Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr
 195 200 205
 Met Ile Gln Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys
 210 215 220
 Asn Ser Gln Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met
 225 230 235 240

Glu Leu Lys Leu Lys Gly Leu Glu Leu Ile Ser Thr Leu Lys Asp
 245 250 255
 Thr Lys Gly Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu
 260 265 270
 Leu Arg Leu Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys
 275 280 285
 Glu Glu Ile Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr
 290 295 300
 Ile Ser Ser Leu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu
 305 310 315 320
 Glu Arg Gln Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln
 325 330 335
 Leu Asp Ile Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala Gln
 340 345 350
 Lys Phe Glu Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu Pro Leu
 355 360 365
 Pro Asn Gln Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu Asn Ile Arg
 370 375 380
 Ile Ile Leu Glu Thr Arg Ala Thr Cys Lys Ser Leu Glu Glu Lys Leu
 385 390 395 400
 Lys Glu Lys Glu Ser Ala Leu Arg Leu Ala Glu Gln Asn Ile Leu Ser
 405 410 415
 Arg Asp Lys Val Ile Asn Glu Leu Arg Leu Arg Leu Pro Ala Thr Ala
 420 425 430
 Glu Arg Glu Lys Leu Ile Ala Glu Leu Gly Arg Lys Glu Met Glu Pro
 435 440 445
 Lys Ser His His Thr Leu Lys Ile Ala His Gln Thr Ile Ala Asn Met
 450 455 460
 Gln Ala Arg Leu Asn Gln Lys Glu Glu Val Leu Lys Lys Tyr Gln Arg
 465 470 475 480
 Leu Leu Glu Lys Ala Arg Glu Glu Gln Arg Glu Ile Val Lys Lys His
 485 490 495
 Glu Glu Asp Leu His Ile Leu His His Arg Leu Glu Leu Gln Ala Asp
 500 505 510
 Ser Ser Leu Asn Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln
 515 520 525
 Ser Pro Thr Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu
 530 535 540
 Met Glu Gln Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu
 545 550 555 560
 Val Lys Leu Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile
 565 570 575
 Thr Glu Leu Lys Val Lys Glu Phe Glu Asn Ile Lys Leu Gln Leu Gln
 580 585 590
 Glu Asn His Glu Asp Glu Val Lys Lys Val Lys Ala Glu Val Glu Asp
 595 600 605
 Leu Lys Tyr Leu Leu Asp Gln Ser Gln Lys Glu Ser Gln Cys Leu Lys
 610 615 620
 Ser Glu Leu Gln Ala Gln Lys Glu Ala Asn Ser Arg Ala Pro Thr Thr
 625 630 635 640
 Thr Met Arg Asn Leu Val Glu Arg Leu Lys Ser Gln Leu Ala Leu Lys
 645 650 655

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109**110**

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Glu Lys Gln Gln Lys Ala Leu Ser Arg Ala Leu Leu Glu Leu Arg Ala
660 665 670

Glu Met Thr Ala Ala Ala Glu Glu Arg Ile Ile Ser Ala Thr Ser Gln
675 680 685

Lys Glu Ala His Leu Asn Val Gln Gln Ile Val Asp Arg His Thr Arg
690 695 700

Glu Leu Lys Thr Gln Val Glu Asp Leu Asn Glu Asn Leu Leu Lys Leu
705 710 715 720

Lys Glu Ala Leu Lys Thr Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp
725 730 735

Asn Leu Asn Asp Leu Asn Asn Glu Leu Gln Lys Lys Gln Lys Ala Tyr
740 745 750

Asn Lys Ile Leu Arg Glu Lys Glu Glu Ile Asp Gln Glu Asn Asp Glu
755 760 765

Leu Lys Arg Gln Ile Lys Arg Leu Thr Ser Gly Leu Gln Gly Lys Pro
770 775 780

Leu Thr Asp Asn Lys Gln Ser Leu Ile Glu Glu Leu Gln Arg Lys Val
785 790 795 800

Lys Lys Leu Glu Asn Gln Leu Glu Gly Lys Val Glu Glu Val Asp Leu
805 810 815

Lys Pro Met Lys Glu Lys Asn Ala Lys Glu Glu Leu Ile Arg Trp Glu
820 825 830

Glu Gly Lys Lys Trp Gln Ala Lys Ile Glu Gly Ile Arg Asn Lys Leu
835 840 845

Lys Glu Lys Glu Gly Glu Val Phe Thr Leu Thr Lys Gln Leu Asn Thr
850 855 860

Leu Lys Asp Leu Phe Ala Lys Ala Asp Lys Glu Lys Leu Thr Leu Gln
865 870 875 880

Arg Lys Leu Lys Thr
885

<210> SEQ ID NO 17
<211> LENGTH: 671
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Ile Leu Thr Lys Glu Ile Asn Lys Leu Glu Leu Lys Ile Ser Asp Phe
1 5 10 15

Leu Asp Glu Asn Glu Ala Leu Arg Glu Arg Val Gly Leu Glu Pro Lys
20 25 30

Thr Met Ile Asp Leu Thr Glu Phe Arg Asn Ser Lys His Leu Lys Gln
35 40 45

Gln Gln Tyr Arg Ala Glu Asn Gln Ile Leu Leu Lys Glu Ile Glu Ser
50 55 60

Leu Glu Glu Glu Arg Leu Asp Leu Lys Lys Ile Arg Gln Met Ala
65 70 75 80

Gln Glu Arg Gly Lys Arg Ser Ala Thr Ser Gly Leu Thr Thr Glu Asp
85 90 95

Leu Asn Leu Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg
100 105 110

Lys Leu Asp Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys
115 120 125

Asn Glu Phe Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu
130 135 140

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Arg Ser Arg Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu
 145 150 155 160
 Val Glu Glu Asn Lys Gln Leu Glu Glu Gly Met Lys Glu Ile Leu Gln
 165 170 175
 Ala Ile Lys Glu Met Gln Lys Asp Pro Asp Val Lys Gly Glu Thr
 180 185 190
 Ser Leu Ile Ile Pro Ser Leu Glu Arg Leu Val Asn Ala Ile Glu Ser
 195 200 205
 Lys Asn Ala Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln
 210 215 220
 Val Asp Gln Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg
 225 230 235 240
 Glu Ser Arg Lys Glu Ala Ile Asn Tyr Ser Gln Gln Leu Ala Lys Ala
 245 250 255
 Asn Leu Lys Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln
 260 265 270
 Ser Glu Gly Ser Asn Val Val Phe Lys Gly Ile Asp Leu Pro Asp Gly
 275 280 285
 Ile Ala Pro Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu
 290 295 300
 Ile His Leu Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn
 305 310 315 320
 Leu Glu Asp Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg
 325 330 335
 His Gln Gln Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr
 340 345 350
 Trp Lys Thr Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu
 355 360 365
 Asp Gln Val Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu
 370 375 380
 Leu Asn Ala Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala
 385 390 395 400
 Gln Ser Gln Lys Glu Ser Gln Cys Leu Lys Ser Glu Leu Gln Ala Gln
 405 410 415
 Lys Glu Ala Asn Ser Arg Ala Pro Thr Thr Thr Met Arg Asn Leu Val
 420 425 430
 Glu Arg Leu Lys Ser Gln Leu Ala Leu Lys Glu Lys Gln Gln Lys Ala
 435 440 445
 Leu Ser Arg Ala Leu Leu Glu Leu Arg Ala Glu Met Thr Ala Ala Ala
 450 455 460
 Glu Glu Arg Ile Ile Ser Ala Thr Ser Gln Lys Glu Ala His Leu Asn
 465 470 475 480
 Val Gln Gln Ile Val Asp Arg His Thr Arg Glu Leu Lys Thr Gln Val
 485 490 495
 Glu Asp Leu Asn Glu Asn Leu Leu Lys Leu Lys Glu Ala Leu Lys Thr
 500 505 510
 Ser Lys Asn Arg Glu Asn Ser Leu Thr Asp Asn Leu Asn Asp Leu Asn
 515 520 525
 Asn Glu Leu Gln Lys Lys Gln Lys Ala Tyr Asn Lys Ile Leu Arg Glu
 530 535 540
 Lys Glu Glu Ile Asp Gln Glu Asn Asp Glu Leu Lys Arg Gln Ile Lys
 545 550 555 560

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Arg Leu Thr Ser Gly Leu Gln Gly Lys Pro Leu Thr Asp Asn Lys Gln
565 570 575

Ser Leu Ile Glu Glu Leu Gln Arg Lys Val Lys Lys Leu Glu Asn Gln
580 585 590

Leu Glu Gly Lys Val Glu Glu Val Asp Leu Lys Pro Met Lys Glu Lys
595 600 605

Asn Ala Lys Glu Glu Leu Ile Arg Trp Glu Glu Gly Lys Lys Trp Gln
610 615 620

Ala Lys Ile Glu Gly Ile Arg Asn Lys Leu Lys Glu Lys Glu Gly Glu
625 630 635 640

Val Phe Thr Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp Leu Phe Ala
645 650 655

Lys Ala Asp Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu Lys Thr
660 665 670

<210> SEQ ID NO 18

<211> LENGTH: 572

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Thr Glu Asn Ile Ser Gln Gly Asp Arg Ile Ser Glu Arg Lys Leu Asp
1 5 10 15

Leu Leu Ser Leu Lys Asn Met Ser Glu Ala Gln Ser Lys Asn Glu Phe
20 25 30

Leu Ser Arg Glu Leu Ile Glu Lys Glu Arg Asp Leu Glu Arg Ser Arg
35 40 45

Thr Val Ile Ala Lys Phe Gln Asn Lys Leu Lys Glu Leu Val Glu Glu
50 55 60

Asn Lys Gln Leu Glu Glu Gly Met Lys Glu Ile Leu Gln Ala Ile Lys
65 70 75 80

Glu Met Gln Lys Asp Pro Asp Val Lys Gly Gly Glu Thr Ser Leu Ile
85 90 95

Ile Pro Ser Leu Glu Arg Leu Val Asn Ala Ile Glu Ser Lys Asn Ala
100 105 110

Glu Gly Ile Phe Asp Ala Ser Leu His Leu Lys Ala Gln Val Asp Gln
115 120 125

Leu Thr Gly Arg Asn Glu Glu Leu Arg Gln Glu Leu Arg Glu Ser Arg
130 135 140

Lys Glu Ala Ile Asn Tyr Ser Gln Gln Leu Ala Lys Ala Asn Leu Lys
145 150 155 160

Ile Asp His Leu Glu Lys Glu Thr Ser Leu Leu Arg Gln Ser Glu Gly
165 170 175

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

Ser Ser Ala Ser Ile Ile Asn Ser Gln Asn Glu Tyr Leu Ile His Leu
195 200 205

Leu Gln Glu Leu Glu Asn Lys Glu Lys Lys Leu Lys Asn Leu Glu Asp
210 215 220

Ser Leu Glu Asp Tyr Asn Arg Lys Phe Ala Val Ile Arg His Gln Gln
225 230 235 240

Ser Leu Leu Tyr Lys Glu Tyr Leu Ser Glu Lys Glu Thr Trp Lys Thr
245 250 255

Glu Ser Lys Thr Ile Lys Glu Glu Lys Arg Lys Leu Glu Asp Gln Val
260 265 270

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Gln Gln Asp Ala Ile Lys Val Lys Glu Tyr Asn Asn Leu Leu Asn Ala
 275 280 285
 Leu Gln Met Asp Ser Asp Glu Met Lys Lys Ile Leu Ala Gln Ser Gln
 290 295 300
 Lys Glu Ser Gln Cys Leu Lys Ser Glu Leu Gln Ala Gln Lys Glu Ala
 305 310 315 320
 Asn Ser Arg Ala Pro Thr Thr Met Arg Asn Leu Val Glu Arg Leu
 325 330 335
 Lys Ser Gln Leu Ala Leu Lys Glu Lys Gln Lys Ala Leu Ser Arg
 340 345 350
 Ala Leu Leu Glu Leu Arg Ala Glu Met Thr Ala Ala Ala Glu Glu Arg
 355 360 365
 Ile Ile Ser Ala Thr Ser Gln Lys Glu Ala His Leu Asn Val Gln Gln
 370 375 380
 Ile Val Asp Arg His Thr Arg Glu Leu Lys Thr Gln Val Glu Asp Leu
 385 390 395 400
 Asn Glu Asn Leu Leu Lys Leu Lys Glu Ala Leu Lys Thr Ser Lys Asn
 405 410 415
 Arg Glu Asn Ser Leu Thr Asp Asn Leu Asn Asp Leu Asn Asn Glu Leu
 420 425 430
 Gln Lys Lys Gln Lys Ala Tyr Asn Lys Ile Leu Arg Glu Lys Glu Glu
 435 440 445
 Ile Asp Gln Glu Asn Asp Glu Leu Lys Arg Gln Ile Lys Arg Leu Thr
 450 455 460
 Ser Gly Leu Gln Gly Lys Pro Leu Thr Asp Asn Lys Gln Ser Leu Ile
 465 470 475 480
 Glu Glu Leu Gln Arg Lys Val Lys Lys Leu Glu Asn Gln Leu Glu Gly
 485 490 495
 Lys Val Glu Glu Val Asp Leu Lys Pro Met Lys Glu Lys Asn Ala Lys
 500 505 510
 Glu Glu Leu Ile Arg Trp Glu Glu Gly Lys Lys Trp Gln Ala Lys Ile
 515 520 525
 Glu Gly Ile Arg Asn Lys Leu Lys Glu Lys Glu Gly Glu Val Phe Thr
 530 535 540
 Leu Thr Lys Gln Leu Asn Thr Leu Lys Asp Leu Phe Ala Lys Ala Asp
 545 550 555 560
 Lys Glu Lys Leu Thr Leu Gln Arg Lys Leu Lys Thr
 565 570

<210> SEQ ID NO 19

<211> LENGTH: 801

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Pro Pro Asn Ile Asn Trp Lys Glu Ile Met Lys Val Asp Pro Asp
 1 5 10 15
 Asp Leu Pro Arg Gln Glu Glu Leu Ala Asp Asn Leu Leu Ile Ser Leu
 20 25 30
 Ser Lys Val Glu Val Asn Glu Leu Lys Ser Glu Lys Gln Glu Asn Val
 35 40 45
 Ile His Leu Phe Arg Ile Thr Gln Ser Leu Met Lys Met Lys Ala Gln
 50 55 60
 Glu Val Glu Leu Ala Leu Glu Glu Val Glu Lys Ala Gly Glu Glu Gln

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65	70	75	80
Ala Lys Phe Glu Asn Gln Leu Lys Thr Lys Val Met Lys Leu Glu Asn			
85	90	95	
Glu Leu Glu Met Ala Gln Gln Ser Ala Gly Gly Arg Asp Thr Arg Phe			
100	105	110	
Leu Arg Asn Glu Ile Cys Gln Leu Glu Lys Gln Leu Glu Gln Lys Asp			
115	120	125	
Arg Glu Leu Glu Asp Met Glu Lys Glu Leu Glu Lys Glu Lys Lys Val			
130	135	140	
Asn Glu Gln Leu Ala Leu Arg Asn Glu Glu Ala Glu Asn Glu Asn Ser			
145	150	155	160
Lys Leu Arg Arg Glu Asn Lys Arg Leu Lys Lys Lys Asn Glu Gln Leu			
165	170	175	
Cys Gln Asp Ile Ile Asp Tyr Gln Ile Asp Ser Gln Lys Glu			
180	185	190	
Thr Leu Leu Ser Arg Arg Gly Glu Thr Glu Asn Ile Ser Gln Gly Asp			
195	200	205	
Arg Ile Ser Glu Arg Lys Leu Asp Leu Leu Ser Leu Lys Asn Met Ser			
210	215	220	
Glu Ala Gln Ser Lys Asn Glu Phe Leu Ser Arg Glu Leu Ile Glu Lys			
225	230	235	240
Glu Arg Asp Leu Glu Arg Ser Arg Thr Val Ile Ala Lys Phe Gln Asn			
245	250	255	
Lys Leu Lys Glu Leu Val Glu Glu Asn Lys Gln Leu Glu Glu Gly Met			
260	265	270	
Lys Glu Ile Leu Gln Ala Ile Lys Glu Met Gln Lys Asp Pro Asp Val			
275	280	285	
Lys Gly Gly Glu Thr Ser Leu Ile Ile Pro Ser Leu Glu Arg Leu Val			
290	295	300	
Asn Ala Ile Glu Ser Lys Asn Ala Glu Gly Ile Phe Asp Ala Ser Leu			
305	310	315	320
His Leu Lys Ala Gln Val Asp Gln Leu Thr Gly Arg Asn Glu Glu Leu			
325	330	335	
Arg Gln Glu Leu Arg Glu Ser Arg Lys Glu Ala Ile Asn Tyr Ser Gln			
340	345	350	
Gln Leu Ala Lys Ala Asn Leu Lys Ile Asp His Leu Glu Lys Glu Thr			
355	360	365	
Ser Leu Leu Arg Gln Ser Glu Gly Ser Asn Val Val Phe Lys Gly Ile			
370	375	380	
Asp Leu Pro Asp Gly Ile Ala Pro Ser Ser Ala Ser Ile Ile Asn Ser			
385	390	395	400
Gln Asn Glu Tyr Leu Ile His Leu Leu Gln Glu Leu Glu Asn Lys Glu			
405	410	415	
Lys Lys Leu Lys Asn Leu Glu Asp Ser Leu Glu Asp Tyr Asn Arg Lys			
420	425	430	
Phe Ala Val Ile Arg His Gln Gln Ser Leu Leu Tyr Lys Glu Tyr Leu			
435	440	445	
Ser Glu Lys Glu Thr Trp Lys Thr Glu Ser Lys Thr Ile Lys Glu Glu			
450	455	460	
Lys Arg Lys Leu Glu Asp Gln Val Gln Gln Asp Ala Ile Lys Val Lys			
465	470	475	480
Glu Tyr Asn Asn Leu Leu Asn Ala Leu Gln Met Asp Ser Asp Glu Met			
485	490	495	

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Lys Lys Ile Leu Ala Glu Asn Ser Arg Lys Ile Thr Val Leu Gln Val
 500 505 510

Asn Glu Lys Ser Leu Ile Arg Gln Tyr Thr Thr Leu Val Glu Leu Glu
 515 520 525

Arg Gln Leu Arg Lys Glu Asn Glu Lys Gln Lys Asn Glu Leu Leu Ser
 530 535 540

Met Glu Ala Glu Val Cys Glu Lys Ile Gly Cys Leu Gln Arg Phe Lys
 545 550 555 560

Glu Met Ala Ile Phe Lys Ile Ala Ala Leu Gln Lys Val Val Asp Asn
 565 570 575

Ser Val Ser Leu Ser Glu Leu Glu Leu Ala Asn Lys Gln Tyr Asn Glu
 580 585 590

Leu Thr Ala Lys Tyr Arg Asp Ile Leu Gln Lys Asp Asn Met Leu Val
 595 600 605

Gln Arg Thr Ser Asn Leu Glu His Leu Glu Cys Glu Asn Ile Ser Leu
 610 615 620

Lys Glu Gln Val Glu Ser Ile Asn Lys Glu Leu Glu Ile Thr Lys Glu
 625 630 635 640

Lys Leu His Thr Ile Glu Gln Ala Trp Glu Gln Glu Thr Lys Leu Gly
 645 650 655

Asn Glu Ser Ser Met Asp Lys Ala Lys Lys Ser Ile Thr Asn Ser Asp
 660 665 670

Ile Val Ser Ile Ser Lys Lys Ile Thr Met Leu Glu Met Lys Glu Leu
 675 680 685

Asn Glu Arg Gln Arg Ala Glu His Cys Gln Lys Met Tyr Glu His Leu
 690 695 700

Arg Thr Ser Leu Lys Gln Met Glu Glu Arg Asn Phe Glu Leu Glu Thr
 705 710 715 720

Lys Phe Ala Glu Leu Thr Lys Ile Asn Leu Asp Ala Gln Lys Val Glu
 725 730 735

Gln Met Leu Arg Asp Glu Leu Ala Asp Ser Val Ser Lys Ala Val Ser
 740 745 750

Asp Ala Asp Arg Gln Arg Ile Leu Glu Leu Glu Lys Asn Glu Met Glu
 755 760 765

Leu Lys Val Glu Val Ser Lys Leu Arg Glu Ile Ser Asp Ile Ala Arg
 770 775 780

Arg Gln Val Glu Ile Leu Asn Ala Gln Gln Ser Arg Asp Lys Glu
 785 790 795 800

Val

<210> SEQ ID NO 20

<211> LENGTH: 3900

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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gccaaaggta accaacataa tgtctcttta caactgagtg aggctactgc tcttggttaag    120
ttggagtc aaatcatctaa actgcagaag atggaggcct acaacttgcg ctttagagcag     180
aaaacttgatg aaaaagaaca ggctcttat tatgctcggt tggaggaaag aaacagagca    240
aaacatctgc gccaacaat tcagtcata cgacgacagt tttagtggagc tttacccttg    300
gcacacaacagg aaaagtctc caaaacaatg attcaactac aaaatgacaa acttaagata   360

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atgcaagaaa tgaaaaattc tcaacaagaa catagaaata tggagaacaa aacattggag	420
atggaattaa aattaaaggc cctgaaagag ttaataaagca cttaaaggc taccaaagga	480
gcccaaagg taatcaactg gcatatgaaa atagaagaac ttgcgtttca agaacttaaa	540
ctaaatcgaa aatttagtcaa ggataaagaa gaaataaaat atttgaataa cataatttc	600
gaatatgaac gtacaatcag cagtcttgc aaagaaattt tgcaacagaa caagtttcat	660
gaagaaaagc aaatggccctg ggttcaaga gaagttgacc tggaacgcca actagacatt	720
tttgaccgtc agcaaatgaa aatactaaat gcccacaaa agtttgcaga agctacagga	780
tcaatccctg acccttagttt gccccttcca aatcaacttg agatcgctt aaggaaaatt	840
aaggagaaca ttcaataat tctagaaaca cgggcaactt gcaaatcaact agaagagaaa	900
ctaaaagaga aagaatctgc tttaagggtt gcaacaacaa atatactgtc aagagacaaa	960
gttatcaatg aactgaggct tcgattgcct gccactgcag aaagagaaaa gctcatagct	1020
gagctaggca gaaaagagat ggaacccaaa ttcaccaca cattgaaaat tgctcatcaa	1080
accattgcaaa acatgcaagc aagggttaat caaaaagaag aagtattaa gaagtatcaa	1140
cgtcttctag aaaaagccag agaggagca agagaaattt tgaagaaaca tgagaaagac	1200
tttcatattt ttcatcacag attagaacta caggctgata gttcaactaa taaattcaaa	1260
caaacggctt gggatttaat gaaacagtct cccactccag ttccatccaa caagcattt	1320
attcgtctgg ctgagatgga acagacagta gcagaacaag atgactctt ttccactc	1380
tttgtcaaac taaagaaatc atcacaagat ttggagagac aaagagaaaat cactgaatta	1440
aaagtaaaag aatttgcata tatcaaatta cagttcaag aaaaccatga agatgaagt	1500
aaaaaaatgaa aagcggaaatc agaggattt aagtatctt tggaccagtc acaaaaggag	1560
tcacagtgtt taaaatctga acttcaggct caaaaagaag caaattcaag agctccaaca	1620
actacaatgaa gaaatcttagt agaacggcta aagagccat tagccttgc ggagaaacaa	1680
cagaaagcac ttatcgccc acttttagaa ctccggcag aaatgacagc agctgctgaa	1740
gaacgttata ttctgcac ttctcaaaaa gaggccatc tcaatgttca acaaattcggt	1800
gatcgacata ctagagagct aaagacacaa gttgaagatt taaatgaaa ttctttaaa	1860
ttgaaagaag cacttaaaac aagtaaaaac agagaaaact cactaactga taatttgaat	1920
gacttaaata atgaactgca aaagaaacaa aaagcctata ataaaataact tagagagaaa	1980
gaggaaattt atcaagagaa tgatgactt aaaaaggact aaccagggtt	2040
ttacaggggca aacccttgc acataataaa caaagtctaa ttgaagaact ccaaaggaaa	2100
tttaaaaaac tagagaacca attagaggga aagggtggagg aagtagacact aaaacctatg	2160
aaagaaaaga atgctaaaga agaattaatt aggtggaaag aagttttttt gtggcaagcc	2220
aaaaatagaag gaattcgaaa caagttaaaa gagaagagg gggaaatctt tactttaca	2280
aagcagttga atactttgaa ggatctttt gccaaagccg ataaagagaa acttactttt	2340
cagagggaaac taaaacaac tggcatgact gttgatcagg tttggaaat acgagcttgc	2400
gagtcgaaa aagaatttggaa agaattttt aagagaaatc ttgacttgc aatgtatata	2460
ttgtatgtt gggccacca agctcttctt cgagattctt ttgttgcataa aatgtatata	2520
caaaaatgtt acctccaaga aaaacttcat gctttttttt aacagtttttca aaggatata	2580
tattctaaatc cttcaatttc aggaatagag tcagatgatc attgtcagag agaacaggag	2640
cttcagaagg aaaacttgaa gttgtcatct gaaaatatttgc aactgaaattt tcagttgaa	2700

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caagcaaata aagatttgcc aagattaaag aatcaagtca gagattgaa ggaaatgtgt	2760
gaatttctta agaaaagaaaa agcagaagtt cagcgaaac ttggccatgt tagagggct	2820
ggtagaaagt gaaagacaat cccagaactg gaaaaaccac ttggttaat gaaaaaagta	2880
gttggaaaag tccagagaga aaatgaacag ttggggaaag catcaggaat attgactgt	2940
gaaaaatgg ctaatattga gcaggaaat gaaaaattga aggctgatt agaaaaactt	3000
aaagctcatc ttggccatca gttgagcatg cactatgaat ccaagacca aggcacagaa	3060
aaaattattg ctgaaaatga aaggcttcgt aaagaactta aaaaagaac tgatgctgca	3120
gagaaattac ggtatgcata gaataattt aagatattaa atgagaagat gacagttcaa	3180
ctagaagaga ctggtaagag attgcagtt gcagaaagca gaggtccaca gcttgaaggt	3240
gctgacagta agagctggaa atccattgtg gttacaagaa tgtatgaaac caagttaaaa	3300
gaattggaaa ctgatattgc caaaaaaaaaa caaagcatta ctgaccttaa acagcttcta	3360
aaagaagcaa cagagagaga acaaaaagtt aacaaataca atgaagacct tgaacaacag	3420
attaagattc ttaaacatgt tcctgaaagg gctgagacag agcaaggcct taaacggag	3480
cttcaagtcc tttagattgc taatcatcg ctggataaa agaaagcaga attaattccat	3540
cagatagaag ctaacaagga ccaaagtgg gctgaaagca ccataacctga tgctgatcaa	3600
ctaaaggaaa aaataaaaga tcttagagaca cagctcaaaa tgtcagatct agaaaagcag	3660
catttgaagg agggaaataaa gaagctgaaa aaagaactgg aaaatttga tccttcattt	3720
tttgaagaaa ttgaagatct taagtataat tacaagggaa aagtgaagaa gaatattctc	3780
tttgaagaga aggtaaaaaa acttcagaa caattggag ttgaattAAC tagccctgtt	3840
gctgcttcgt aagagtttga agatgaagaa gaaagtccctg ttaattccc catttactaa	3900

<210> SEQ ID NO 21

<211> LENGTH: 1200

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

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gaggcactta gagagcgtgt gggccttcaa ccaaagacaa tgattgattt aactgaattt	120
agaaatagca aacacttaaa acacgacgac tacagagctg aaaaccatgt tctttgaaa	180
gagattgaaa gtcttagagga agaacgactt gatctgaaaa aaaaattcg tcaaattggct	240
caagaaaagag gaaaaagaag tgcaacttca ggattaacca ctgaggacct gaacctaact	300
gaaaacattt ctcaaggaga tagaataagt gaaagaaaat tggattttt gaggcctcaaa	360
aatatgatgt aacgacaaatc aaagaatgaa ttctttcaa gagaactaat tgaaaaagaa	420
agagatttag aaaggagtag gacagtataa gccaaatttc agaataaattt aaaagaattt	480
tttgaagaaa ataagcaact tgaagaaggt atgaaagaaa tattgcaac aattaaggaa	540
atgcagaaag atcctgtgt taaaaggagga gaaacatctc taattatccc tagccttcaa	600
agacttagtta atgctataga atcaaagaat gcagaaggaa tctttgatgc gatctgcat	660
tttgaagaaa aagttgtatca gcttaccggaa agaaatgaa aatataacca ggagctcagg	720
gaatctcgaa aagaggctat aaattattca cagcagttgg caaaagctaa tttaaagata	780
gaccatcttgc aaaaagaaac tagtcttttca cgacaatcg aaggatcgaa tgggttttt	840
aaaggaaatttgc acttacctgaa tggatagca ccatctgttgc ccagtatcat taattctcg	900
aatgaatattt taatacattt gttacaggaa ctagaaaata aagaaaaaaa gttaaagaaat	960

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tttagaagatt ctcttgaaga ttacaacaga aaatttgctg taattcgtca tcaacaaagt 1020
 ttgttgtata aagaataacct aagtggaaaag gagacctggaa aaacagaatc taaaacaata 1080
 aaagaggaaa agagaaaact tgaggatcaa gtccaaacaag atgctataaa agtaaaagaa 1140
 tataataatt tgctcaatgc tcttcagatg gattcggatg aaatgaaaaa aatacttgca 1200

 <210> SEQ ID NO 22
 <211> LENGTH: 3090
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 22

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 gccaagttgc accaacataa tgtctctt caactggatg aggctactgc tcttggtaag 120
 ttggagtcaa ttacatctaa actgcagaag atggaggcct acaacttgcg cttagagcag 180
 aaacttgcatg aaaaagaaca ggctcttat tatgctcgat tggaggaaag aaacagagca 240
 aaacatctgc gccaaacaat tcagtcctca cgacgacagt ttagtggagc tttacccttg 300
 gcacaacagg aaaagtctc caaaacaatg attcaactac aaaatgacaa acttaagata 360
 atgcaagaaa tgaaaaattc tcaacaagaa catagaaata tggagaacaa aacattggag 420
 atgaaattaa aattaaaggc cctggaaagag ttaataagca ctttaagga taccaaagga 480
 gcccaaaagg taatcaactg gcatatgaaa atagaagaac ttctgtttca agaacttaaa 540
 ctaaatcggg aattagtcaa ggataaagaa gaaataaaat atttgaataa cataattct 600
 gaatatgaac gtacaatcag cagtcttcaa gaagaaattt tgcaacagaa caagtttcat 660
 gaagaaagac aatggcctg ggatcaaaga gaagttgacc tggaacgcca actagacatt 720
 ttgaccgtc agcaaaatga aatactaaat gcggcacaaa agtttgaaga agctacagga 780
 tcaatccctg acccttagttt gcccattca aatcaacttg agatcgctct aaggaaaatt 840
 aaggagaaca ttcaataat tctagaaaca cgggcaactt gcaaatcact agaagagaaa 900
 ctaaaagaga aagaatctgc tttaaggta gcagaacaaa atatactgtc aagagacaaa 960
 gtaatcaatg aactgaggct tcgattgcct gccactgcag aaagagaaaa gctcatagct 1020
 gagctaggca gaaaagagat ggaacccaaa tctcaccaca cattgaaaat tgctcatcaa 1080
 accattgcaac acatgcacgc aaggttaaat caaaaagaag aagtattaaa gaagtatcaa 1140
 cgtcttctag aaaaagccag agaggagcaa agagaaattt tgaagaaaca tgaggaaagac 1200
 ctccatattc ttcatcacag attagaacta caggctgata gttcaactaaa taaattcaaa 1260
 caaacggctt gggatttaat gaaacagtct cccactccag ttccatccaa caagcattt 1320
 attcgtctgg ctgagatgga acagacagta gcagaacaag atgactcttcttccactc 1380
 ttgtcaaac taaagaaaatc atcacaagat ttggagagac aaagagaaaat cactgaatta 1440
 aaagtaaaag aatttggaaa tatcaaattt cagttcaag aaaaccatga agatgaagtg 1500
 aaaaaagtaa aagcggaaatc agaggattt aagtatcttgc tggacacaac tggcatgact 1560
 gttgatcagg ttttggaaat acgagtttgc gagtcgaaaa aagaatttggaa agaattaaaa 1620
 aagagaaaatc ttgactttaga aaatgatata ttgtatata gggccccacca agctcttctt 1680
 cgagattctg ttgttagaaga ttacatttcaaaaatagat acctccaaga aaaacttcat 1740
 gcttttagaaa aacagtttcaaaaggataca tattctaagc ttccatttc aggaatagag 1800
 tcagatgatc attgtcagag agaacaggag ctccagaagg aaaacttgaa gttgtcatct 1860

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gaaaatattt aactgaaatt tcagcttcaa caagcaaata aagatttgcc aagattaaag	1920
aatcaagtca gagatttcaa ggaaatgtgt gaatttcattt agaaagaaaa agcagaagtt	1980
cagcgaaac ttggccatgt tagagggtct ggtagaagtg gaaagacaat cccagaactg	2040
gaaaaaaacca ttggtttaat gaaaaaagta gttgaaaaag tccagagaga aatgaacag	2100
ttgaaaaaaag catcaggaaat attgactgtg gaaaaaatgg ctaatattga gcaggaaaat	2160
gaaaaatttga aggctgaatt agaaaaactt aaagctcatc ttgggcattca gttgagcatg	2220
cactatgaat ccaagaccaa aggcacagaa aaaattattt ctgaaaatga aaggcttcgt	2280
aaagaactta aaaaagaaac tgatgctgca gagaattac ggatagcaaa gaataattta	2340
gagatattaa atgagaagat gacagttcaa ctagaagaga ctggtaagag attgcagtt	2400
gcagaaagca gaggtccaca gcttgaaggt gctgacagta agagctggaa atccatttg	2460
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gctgagacag agcaaggccct taaacgggg cttcaagttc ttagatttc taatcatcag	2700
ctggataaag agaaagcaga attaatccat cagatagaag ctaacaagga ccaaagtgg	2760
gctgaaagca ccatacctga tgctgatcaa ctaaaggaaa aaataaaaga tcttagagaca	2820
cagctcaaaa tgtcagatct agaaaagcag catttgaagg agggaaataaa gaagctgaaa	2880
aaagaactgg aaaatttga tccttcattt ttttgaagaaa ttgaagatct taagtataat	2940
tacaaggaaag aagtgaagaa gaatattctc tttagaagaga aggtaaaaaaa actttcagaa	3000
caattgggag ttgaatataac tagccctgtt gctgcttcgt aagagtttga agatgaagaa	3060
gaaaagtccgt ttaatttccc cattttactaa	3090

<210> SEQ ID NO 23
 <211> LENGTH: 3846
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

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aaaaatatga gtgaagcaca atcaaagaat gaatttcttt caagagaact aattgaaaaaa	120
gaaagagatt tagaaaggag taggacagtg atagccaaat ttcagaataa attaaaagaa	180
ttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaag	240
gaaatgcaga aagatcctga tggtaaaggaa ggagaaacat ctctaattat ccctagcctt	300
gaaaagactag ttaatgttat agaatcaaag aatgcagaag gaatcttga tgcgagtcgt	360
catttggaaag cccaaaggta tcagcttacc ggaagaaatg aagaattaag acaggagctc	420
agggaaatctc ggaaagaggc tataaattat tcacagcagt tggcaaaagc taatttaaag	480
atagaccatc ttgaaaaaga aactagtctt ttacgacaat cagaaggatc gaatgttgc	540
tttaaaggaa ttgacttacc tggatggata gcaccatcta gtgccagtat cattaattct	600
cagaatgaat atttaataca ttgttacag gaacttagaaa ataaagaaaa aaagttaaag	660
aattttagaag attctcttgc agattacaac agaaaatttg ctgttaattcg tcatcaacaa	720
agtttgggtt ataaagaata cctaaatgtgaa aaggagaccc ggaaaacaga atctaaaaca	780
ataaaaagagg aaaagagaaaa acttgaggat caagtccaaac aagatgttat aaaagtaaaa	840
gaatataata atttgctcaa tgctttcgtt atggatttcgtt atgaaatgaa aaaaataactt	900

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gcagaaaata gtaggaaaat tactgttttgc aagtgaatg aaaaatcaact tataaggcaa	960
tataacaacct tagttagaaatt ggagcgacaa cttagaaaag aaaatgagaa gcaaaagaat	1020
gaattgttgt caatggaggc tgaagttgt gaaaaaatttgg ggtgtttgc aagatttaag	1080
gaaatggcca ttttcaagat tgcaagtc caaaaaaaaatgg tagataatag tggttttttg	1140
tctgaactag aactggctaa taaacagtac aatgaactga ctgctaagta cagggacatc	1200
ttgcaaaaag ataataatgct tggtaaaga acaagtaact tggaaacacct ggagtgtgaa	1260
aacatctcct taaaagaaca agtggagtct ataaataaag aactggagat taccaaggaa	1320
aaacttcaca ctattgaaca agcctggaa caggaaacta aatttagttaa tgaatctagc	1380
atggataagg caaagaaaatc aataaccaac agtgacatttgc ttccatttc aaaaaaaaaata	1440
actatgtgg aatgtggaa attaaatgaa aggcagcggg ctgaacatgg tcaaaaaatg	1500
tatgaacact tacggacttc gttaaagcaa atggaggaaac gtaattttga attggaaacc	1560
aaatttgctg agcttaccaa aatcaatttg gatgcacaga aggtggaaaca gatgttaaga	1620
gatgaattag ctgatagtgt gggcaaggca gtaagtgtatc ctgataggca acggattcta	1680
gaatttagaga agaatgaaat ggaactaaaa gttgaagtgt caaaaaaaaactgag agagattct	1740
gatattgcca gaagacaagt tgaaattttgc aatgcacaaac aacaatctgg ggacaaggaa	1800
gtaaaaatgaa aagaagcact taaaacaagt aaaaacagag aaaaactcaact aactgataat	1860
ttgaatgact taaataatgaa actgcaaaag aaacaaaaag cctataataa aatacttaga	1920
gagaaagagg aaattgtatca agagaatgt gaaactgaaaa ggcaaaattaa aagactaacc	1980
agtggattac agggcaaaacc cctgacagat aataaacaacaa gtcttaatttgc agaactccaa	2040
aggaaagttt aaaaactaga gaaccatataa gagggaaagg tggaggaaatg agacccaaaa	2100
cctatgaaag aaaagaatgc taaagaagaa ttaatttagt gggagaagg taaaagttgg	2160
caagccaaaa tagaaggaat tcgaaacaag taaaagaga aagagggggaa agtctttact	2220
ttaacaaacgc agttgaatac ttgtggat ctttttgc aagccgatataa agagaaactt	2280
actttgcaga ggaaactaaa aacaactggc atgactgttgc atcagggtttt gggatacga	2340
gctttggagt cagaaaaaga atttggaaagaa ttaaaaaaaga gaaatcttgc ctttagaaaaat	2400
gatataattgt atatggggc ccaccaagct cttccctcgat attctgttgtt agaagatata	2460
catttacaaa atagataacctt ccaagaaaaa cttcatgtttt tagaaaaaca gttttcaag	2520
gatacatatt ctaagccctt aatttcggat atagagttagt atgatcatgg tcaagagagaa	2580
caggagcttc agaaggaaaa cttgaagttgc tcacatgttcaaa atattgtact gaaatttcag	2640
cttgaacaag caaataaaga tttgccaaga ttaaagaatc aagttagtgc tttgaaggaa	2700
atgtgtgaat ttcttaagaa agaaaaagca gaagttcagc ggaaacttgg ccatgttaga	2760
gggtctggta agagtggaaa gacaatccc gaaactggaaa aaaccatttgg tttatgaaa	2820
aaaagttagttt aaaaagtccaa gagagaaaaat gaacagtgc aaaaagcatc aggaatatttgc	2880
actagtggaaa aaatggctaa tattgagcag gaaaatgaaa aattgtggc tgaatttagaa	2940
aaactttaag ctcatottgg gcacatgttgc agcatgcact atgaatccaa gaccaaggc	3000
acagaaaaaa ttattgtgc aatgaaaagg cttcgtaaag aactttaaaaa agaaactgtat	3060
gctgcagaga aattacggat agcaaaagaat aatttagaga tattaaatgaa gaaatgtac	3120
gttcaacttag aagagacttgc taagagatttgc cagtttgcag aaagcagagg tccacagctt	3180
gaagggtctg acagtaagag ctggaaatcc attgtggta caagaatgtc tgaaaccaag	3240

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ttaaaaagaat tggaaactga tattgccaaa aaaaatcaaa gcattactga ccttaaacag	3300
cttgtaaaag aagcaacaga gagagaacaa aaagttaaca aatacaatga agaccttgaa	3360
caacagatta agattcttaa acatgttcct gaaggtgctg agacagagca aggcttaaa	3420
cgggagctc aagttcttag attagcta catcagctgg ataaagagaa agcagaatta	3480
atccatcaga tagaagctaa caaggacaa agtggagctg aaagcaccat acctgtatgc	3540
gatcaactaa aggaaaaat aaaagatcta gagacacagc tcaaaaatgtc agatctagaa	3600
aagcagcatt tgaaggagga aataaagaag ctgaaaaaag aactggaaaa ttttgcatt	3660
tcatttttg aagaaattga agatcttaag tataattaca aggaagaat gaagaagaat	3720
attctcttag aagagaaggt aaaaaaactt tcagaacaat tggagttga attaactagc	3780
cctgttgctg cttctgaaga gtttgaagat gaagaagaaa gtcctgttaa tttccccatt	3840
tactaa	3846

<210> SEQ ID NO 24
<211> LENGTH: 2358
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24	
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gccaagttgc accaacataa tgtctctt caactgatgtt aggctactgc tcttggttaag	120
ttggagtc aa ttacatctaa actgcagaag atggaggccat acaacttgcg ctttagagcag	180
aaaccttgc aaaaagaaca ggctctctat tatgctcggtt tggagggaag aaacagagca	240
aaacatctgc gccaaacaat tcagtctcta cgacgcacagt ttagtggagc tttacccttgc	300
gcacaacagg aaaagtctc caaaaacatgc attcaactac aaaatgcacaa acttaagata	360
atgcaagaaa tgaaaaattc tcaacaagaa catagaaata tggagaacaa aacattggag	420
atgaaattaa aattaaaggc ccttggagag ttaataagca cttttaagga taccaagga	480
gcccggaaagg taatcaactg gcatatgaaa atagaagaac ttctgtttca agaacttaaa	540
ctaaatcgaa aatttgtcaa ggataaagaa gaaataaaat atttgaataa cataatttct	600
gaatatgaac gtacaatcag cagtcttgcgaa gaagaaattt tgcaacagaa caagtttcat	660
gaagaaagac aaatggccctg ggttcaaaaga gaagttgacc ttggaaacgcca actagacatt	720
tttgaccgtc agcaaatgc aatactaaat gcggcacaaa agtttgcgaa agctacagga	780
tcaatccctg accctgtttt gccccttcca aatcaacttg agatcgctt aaggaaaattt	840
aaggagaaca ttcaataat tcttagaaaca cggcaactt gcaaatcact agaagagaaa	900
ctaaagaga aagaatctgc tttaagggtt gcagaacaaa atatactgtc aagagacaaa	960
gtaatcaatg aactgaggct tcgattgcct gccactgcag aaagagaaaa gctcatagct	1020
gagctaggca gaaaagagat ggaaccaaaa tctcaccaca cattgaaaat tgctcatcaa	1080
accattgcacaa acatgcacgc aaggtaaat caaaaagaag aagtattaa gaagtttcaaa	1140
cgtcttcttag aaaaagccag agaggagcaaa agagaaattt tgaagaaaca tgagggagac	1200
cttcatattc ttcatcacag attagaacta caggctgata gtttactaaa taaattcaaa	1260
caaacggctt gggatttaat gaaacagtct cccactccag ttccatccaa caagcatttt	1320
attcgtctgg ctgagatggc acagacatgtt gcaacaacaa atgactctt ttccatccatc	1380
ttggtcaac taaagaaaatc atcacaagat ttggagagac aaagagaaaat cactgaatta	1440
aaagtaaaaatc aatttgcacaa tatcaaaatca cagttcaag aaaaccatgc agatgcgt	1500

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aaaaaaagtta aagcggagt agaggattt aagtatcttc tggaccagtc acaaaaggag	1560
tcacagtgtt taaaatctga acttcaggct caaaaagaag caaattcaag agctccaaca	1620
actacaatga gaaatctagt agaacggcta aagagccat tagccttcaa ggagaaacaa	1680
cagaaagcac tttagcgggc acttttagaa ctccgggcaag aaatgacagc agctgctgaa	1740
gaacgttata tttctgcaac ttctcaaaaa gaggcccatt tcaatgttca acaaatcggt	1800
gatcgacata ctagagagct aaagacacaa gttgaagatt taaatgaaaa tcttttaaaa	1860
ttgaaagaag cactaaaaac aagtaaaaaac agagaaaaact cactaactga taatttgaat	1920
gacttaata atgaactgca aaagaaacaa aaaggctata ataaaataact tagagagaaa	1980
gaggaaattt atcaagagaa tgatgaactg aaaaggcaaa taaaagact aaccagtgg	2040
ttacaggcga aaccctgac agataataaa caaagtctaa ttgaagaact ccaaaggaaa	2100
gttaaaaaac tagagaacca attagaggg aaggtggagg aagtagaccc aaaaacctatg	2160
aaagaaaaaga atgctaaaga agaattaatt aggtgggaag aagttaaaaa gtggcaagcc	2220
aaaatagaag gaattcgaaa caagttaaaa gagaaagagg gggaaagtctt tactttaaca	2280
aagcagttga atactttgaa ggatctttt gccaaagccg ataaagagaa acttactttg	2340
cagagggaaac taaaaaca	2358

<210> SEQ ID NO 25

<211> LENGTH: 2745

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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gaggcactta gagagegtgt gggcatttcaa ccaaagacaa tgattgattt aactgaattt	120
agaaatagca aacacttaaa acagcagcag tacagagctg aaaaccagat tctttgaaa	180
gagattgaaa gtcttagagga agaacgactt gatctgaaaa aaaaaattcg tcaaattggct	240
caagaaaagag gaaaaaagaag tgcaacttca ggattaacca ctgaggaccc gaaacctact	300
gaaaacattt ctcaaggaga tagaataagt gaaagaaaaat tggatttatt gagcctcaaa	360
aatatgagtg aagcacaatc aaagaatgaa tttctttcaa gagaactaat tggaaaaagaa	420
agagatttag aaaggagtag gacagtgata gccaaatttc agaataaatt aaaagaatta	480
tttgaagaaa ataagcaact tgaagaaggt atgaaagaaaa tattgcaagc attaaggaa	540
atgcagaaag atcctgtatgt taaaggagga gaaacatctc taattatccc tagcatttcaa	600
agacttagtta atgctataga atcaaagaat gcagaaggaa tctttgatgc gagtctgcat	660
tttggaaagccc aagttgatca gcttaccggaa agaaatgaa gatataagaca ggagtcagg	720
gaatctcgaa aagaggctat aaattattca cagcagttgg caaaagctaa tttaaagata	780
gaccatcttgg aaaaagaaaac tagtcttttca cgacaatcag aaggatcgaa tgggttttt	840
aaaggaatttgc tttagatgc ccatcttagtg ccagtatcat taattctcag	900
aatgaatatt taatacattt gttacaggaa ctagaaaata aagaaaaaaa gttaaagaat	960
ttagaaagattt ctcttgcaga ttacaacaga aaatttgcgtt taattcgtca tcaacaatgt	1020
tttgtgtata aagaataacct aagtggaaaag gagacctggaa aacagaatc taaaacaata	1080
aaaagggaaa agagaaaaact tgaggatcaa gtccaaacaag atgctataaa agtggaaa	1140
tataataatt tgctcaatgc tcttcagatg gattcggatg aaatgaaaaa aataacttgca	1200

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acaactggca tgactgttga tcaggtttg ggaatacgag ctttgagtc agaaaaagaa	1260
ttgaaaat taaaaaagag aaatcttgc tttagaaaatg atatatttta tatggggcc	1320
caccaagctc ttccctcgaga ttctgttga gaagattac atttacaaaa tagatacctc	1380
caagaaaaac ttcatgtttt agaaaaacag ttttcaaagg atacatattc taagecctca	1440
atttcaggaa tagagtca tgatcattgt cagagagaac aggagctca gaaggaaaac	1500
ttgaagttt catctaaaaa tattgaactg aaatttcagc ttgaacaagc aaataaaagat	1560
ttgccaaat taaagaatca agtcagagat ttgaaggaaa tgtgtgaatt tcttaagaaa	1620
aaaaaaagcag aagttcagcg gaaacttgcg catgttagag ggtctggtag aagtggaaag	1680
acaatcccag aactggaaaaa aaccatttgtt ttaatgaaaa aagttagttga aaaagtccag	1740
agagaaaaatg aacagtggaa aaaagcatca ggaatattga ctatgtaaaa aatggctaat	1800
attgagcagg aaaatgaaaaa attgaaggct gaatttagaaa aacttaaagc tcatcttggg	1860
catcagttga gcatgcacta tgaatccaag accaaaggca cagaaaaat tattgctgaa	1920
aatgaaaaggc ttcgtaaaga actaaaaaaa gaaactgtat ctgcagagaa attacggata	1980
gcaaaaataa atttagagat attaaatgag aagatgacat ttcaactaga agagactgg	2040
aagagattgc agtttgcaga aagcagaggt ccacagcttgc aaggtgtcga cagtaagagc	2100
tggaaatcca ttgtggttac aagaatgtat gaaaccaagt taaaagaatt ggaaactgtat	2160
attgccccaaa aaaatcaaag cattactgac cttaaacagc ttgtaaaaa agcaacagag	2220
agagaacaaa aagttaacaa atacaatgaa gacctgaaac aacagattaa gattctaaa	2280
catgttcctg aaggtgtcga gacagagca ggccttaaac gggagctca agttttaga	2340
ttagctaattc atcagctggaa taaagagaaa gcagaattaa tccatcagat agaagctaac	2400
aaggacacaaa gtggagctga aagcaccata cctgtatgtc atcaactaaa ggaaaaataa	2460
aaagatctag agacacagct caaaatgtca gatcttagaaa agcagcattt gaaggaggaa	2520
ataaagaagc taaaaaaaaga actggaaaaat ttgtatcctt catttttta agaaaattgaa	2580
gatcttaagt ataattacaa ggaagaagtg aagaagaata ttctttaga agagaaggta	2640
aaaaaaaaactt cagaacaattt gggagttgaa ttaacttagcc ctgtgtcgtc ttctgaagag	2700
tttgaagatg aagaagaaag tcctgttaat ttccccattt actaa	2745

<210> SEQ ID NO 26

<211> LENGTH: 2655

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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gaggcactta gagagcgtgt gggccttggaa ccaaagacaa tgattgattt aactgaattt	120
agaaatagca aacactttaa acagcagcag tacagagctg aaaaccatgt tcttttggaa	180
gagattgaaa gtcttagagga agaacgactt gatctgaaaa aaaaaattcg tcaaattggct	240
caagaaaaagag gaaaaaagaag tgcaacttca ggattaacca ctgaggacct gAACCTAGAG	300
tccctcagaa tgcaactgtc agactatcg gcacagctg atgaaaaatgc gctcattgcc	360
aagttgcacc aacataatgt ctcttttcaa ctgagtgagg ctactgtct tggtaagttg	420
gagtcaatta catctaaaact gcagaagatg gaggcctaca acttgcgtt agagcagaaaa	480
cttggatgaaa aagaacaggc tctcttattt gctcggttgg agggaaagaaa cagagcaaaa	540
catctgcgcc aaacaattca gtctctacga cgacagtttgc tggagctt acccttggca	600

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caacaggaaa agttctccaa aacaatgatt caactacaaa atgacaaaact taagataatg	660
caagaaaatga aaaattctca acaagaacat agaaatatgg agaacaaaac attggagatg	720
gaattaaaaat taaagggcct ggaagagttt ataagcactt taaaggatac caaaggagcc	780
caaaaggtta tcaactggca tatgaaaata gaagaacttc gtcttcaaga actttaacta	840
aatcgaaaat tagtcaagga taaaagaagaa ataaaatatt tgaataacat aatttctgaa	900
tatgaacgta caatcagcag tccttgaagaa gaaaattgtgc aacagaacaa gtttcatgaa	960
gaaaagacaaa tggcctggga tcaaagagaa gttgacctgg aacgccaact agacatttt	1020
gaccgtcagc aaaatgaaat actaaatgcg gcacaaaagt ttgaagaagc tacaggatca	1080
atcccctgacc ctagtttgcc ccttccaaat caacttgaga tcgctctaag gaaaattaag	1140
gagaacattc gaataattct agaaaacacgg gcaacttgca aatcactaga agagaaacta	1200
aaagagaaaag aatctgctt aaggtagca gaacaaaata tactgtcaag agacaaagta	1260
atcaatgaac tgaggcttcg attgcctgcc actgcagaaa gagaaaagct catagctgag	1320
ctaggcagaa aagagatgga accaaaatct caccacacat tgaaaattgc tcatcaaacc	1380
attgcaaca tgcaagcaag gttaaatcaa aaagaagaag tattaaagaa gtatcaacgt	1440
cttctagaaa aagccagaga ggagoaaaga gaaaattgtga agaaacatga ggaagacctt	1500
catattcttc atcacagatt agaactacag gctgatagtt cactaaataa attcaaacaa	1560
acggcttggg atttaatgaa acagtctccc actccagttc ctaccaacaa gcattttatt	1620
cgtctggctg agatgaaaca gacagtagca gaacaagatg actctcttc ctcactcttgc	1680
gtcaaactaa agaaagtatc acaagattt gagagacaaa gagaaatcac tgaattaaaa	1740
gtaaaagaat ttgaaaatat caaattacag cttaagaaaa accatgaaga tgaagtgaaa	1800
aaagtaaaag cggaagtaga ggatttaag tatcttctgg accagtcaca aaaggagtca	1860
cagtgtttaa aatctgaact tcaggctcaa aaagaagcaa attcaagagc tccaacaact	1920
acaatgagaa atcttagtaga acggctaaag agccaattag ctttgaagga gaaacaacag	1980
aaagcactta gtcgggcaact ttttagactc cgggcagaaa tgacagcagc tgctgaagaa	2040
cgttattttt ctgcaacttc tcaaaaagag gccccatctca atgttcaaca aatcggttat	2100
cgacatacta gagagctaa gacacaagtt gaagattta atgaaaatct tttaaaatttgc	2160
aaagaagcac taaaacaag taaaacaga gaaaactcac taactgataa tttgaatgac	2220
ttaaataatg aactgaaaaa gaaacaaaaa gcctataata aaatacttag agagaaagag	2280
gaaaattgatc aagagaatga tgaactgaaa aggcaaattt aaagactaac cagtggat	2340
caggccaaac ccctgacaga taataaacaa agtctaattt aagaactcca aaggaaagtt	2400
aaaaaaacttag agaaccattt agggggaaag gtggagggaa tagacataaa accttatgaaa	2460
gaaaagaatg ctaaagaaga attaattttgg tgggagaag gtaaaaatgt gcaagccaaa	2520
atagaaggaa ttcgaaacaa gttaaaagag aaagaggggg aagtctttac tttaacaaag	2580
cagttgaata ctgttgaagga tcttttgcc aaagccgata aagagaaact tactttgcag	2640
aggaaaactaa aaaca	2655

<210> SEQ ID NO 27

<211> LENGTH: 2013

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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atattaacaa aggaatcaa taaacttcaa ttgaagatca gtgattcct tgatgaaaat	60
gaggcactta gagagegtgt gggccttcaa ccaaagacaa tgattgattt aactgaattt	120
agaatagca aacacttaaa acagcagcag tacagagctg aaaaccagat tctttgaaa	180
gagattgaaa gtcttagagga agaacgactt gatctgaaaa aaaaaattcg tcaaattggct	240
caagaaaagag gaaaaaagaag tgcaacttca ggattaacca ctgaggactt gaacctaact	300
gaaaacattt ctcaaggaga tagataagt gaaagaaaat tggattttt gaggctcaaa	360
aatatgagtg aagcacaatc aaagaatgaa tttcttcaa gagaactaat tgaaaaagaa	420
agagatttag aaaggagtag gacagtata gccaaatttc agaataaattt aaaagaatta	480
gttgaagaaa ataagcaact tgaagaaggt atgaaagaaa tattgcaagc attaaggaa	540
atgcagaaag atcctgatgt taaaggagga gaaacatctc taattatccc tagccttcaa	600
agactatgtt atgctataga atcaaagaat gcagaaggaa tctttgatgc gagtctgcat	660
ttgaaagccc aagttgatca gcttaccgga agaaatgaaat aattaagaca ggagctcagg	720
gaatctcgga aagaggctat aaattattca cagcagttgg caaaaagctaa tttaaagata	780
gaccatcttggaaaagaaac tagtcttttca cgacaatcga aaggatcgaa tggtgtttt	840
aaaaggaattt acttacatcga tgggatagca ccatcttagt ccagtatcat taattctcag	900
aatgaatattt taatacattt gttacaggaa cttagaaata aagaaaaaaaa gttaaagaaat	960
tttagaagattt ctcttgaaga ttacaacaga aaatttgcgtg taattcgtca tcaacaaagt	1020
tttgtgtata aagaataacctt aagtgaaaag gagacctggaa aaacagaatc taaaacaata	1080
aaagaggaaaa agagaaaaact tgaggatcaa gtccaaacaag atgctataaa agtaaaagaa	1140
tataataattt tgctcaatgc tcttcagatg gattcggatg aaatgaaaaa aatacttgca	1200
cagtcacaaa aggagtccaca gtgtttaaaa tctgaacttc aggctcaaaa agaagcaat	1260
tcaagagctc caacaactac aatgagaaat ctatcgtaaac ggctaaagag ccaattagcc	1320
ttgaaaggaga aacaacagaa agcacttagt cgggcacttt tagaactccg ggcagaaatg	1380
acagcagctg ctgaagaacg tattatttctt gcaacttctc aaaaagaggc ccatctcaat	1440
gttcaacaaa tcgttgcgtc acatactaga gagctaaaga cacaaggatg agattnaat	1500
gaaaatcttt taaaattgaa agaagactt aaaaacaatgaa aaaaacagaga aaactcacta	1560
actgataattt tgaatgactt aaataatgaa ctgcaaaaga aacaaaaaagc ctataataaa	1620
atacttagag agaaagagga aattgatcaa gagaatgtatg aactgaaaag gcaaattaaa	1680
agactaaccatgtt gttttttttt gggcaaaatccc ctgacagata ataaacaaag tctaatttggaa	1740
gaactccaaa ggaaagttaa aaaaacttagag aaccaattttt agggaaaggt ggagggaaat	1800
gacctaaac ctatgaaaga aaagaatgtt aaagaagaat taatttaggtt ggaagaaggt	1860
aaaaagtggc aagccaaaat agaaggaattt cggcaacaatg taaaagagaa agagggggaa	1920
gtctttactt taacaaagca gttgaataact ttgaaggatc tttttgcacaa agccgataaa	1980
gagaaaacttta ctttgcagag gaaaactaaaa aca	2013

<210> SEQ ID NO 28
<211> LENGTH: 1716
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

actgaaaaca tttctcaagg agatagaata agtggaaaat aattggatattt attgagctc	60
aaaaatatgaa gtgaaggcaca atcaaagaat gaatttctt caagagaact aattgaaaaa	120

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gaaagagaggat tagaaaggag taggacagtgc atagccaaat ttcagaataa attaaaagaa	180
ttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaag	240
gaaatgcaga aagatcctga tgttaaagga ggagaaacat ctctaattat ccctagcctt	300
gaaagactag ttaatgctat agaatcaaag aatgcagaag gaatcttgc tgcgagtctg	360
catttggaaag cccaagttga tcagcttacc ggaagaaaatg aagaattaag acaggagctc	420
agggaatctc ggaaagaggc tataaattat tcacagcgt tggcaaaagc taattnaaag	480
atagaccatc ttgaaaaaga aactagtctt ttacgacaat cagaaggatc gaatgttgc	540
tttaaaggaa ttgacttacc tgatggata gcaccatcta gtgccagtat cattaattct	600
cagaatgaat atttataaca tttgttacag gaactagaaa ataaagaaaa aaagttaaag	660
aattttagaaat ttctcttgc agattacaac agaaaatttg ctgttaattcg tcatcaacaa	720
agtttgggtt ataaagaata cctaagtgaa aaggagacct ggaaaacaga atctaaaaca	780
ataaaagagg aaaagagaaa acttgaggat caagtccaaac aagatgttat aaaagtaaaa	840
gaatataata atttgcctaa tgcttccatc atggattcgg atgaaatgaa aaaaatactt	900
gcacagtcac aaaaggagtc acagtgttta aaatctgaaat ttcaggotca aaaagaagca	960
aattcaagag ctccaaacaaac tacaatgaga aatcttagtag aacggctaaa gagccaaatta	1020
gccttgcagg agaaaacaaca gaaagcattt agtcgggcac ttttagaact ccgggcagaa	1080
atgacagcag ctgctgaaatc acgttatttt tctgcaactt ctcaaaaaga ggccatctc	1140
aatgttcaac aaatcggttgc tcgacataact agagagcttta agacacaatg tgaagattt	1200
aatgaaaatc tttaaaattt gaaagaagca cttaaaacaa gtaaaaacag agaaaactca	1260
cttaactgata atttgcattttt cttaataat gaaatgcataa agaaacaaaa agcctataat	1320
aaaatactta gagagaaaaga ggaaattgttcaagagaatg atgaaatgaa aaggcaattt	1380
aaaagactaa ccagtggtt acaggcataa cccctgacatc ataataaaca aagtcttattt	1440
gaagaactcc aaaggaaagt taaaaacta gagaaccaat tagagggaaa ggtggaggaa	1500
gttagacctaa aacctatgaa agaaaagaat gctaaagaag aattaattttt gttggaaagaa	1560
ggtaaaaagt ggcaagccaa aatagaagga attcgaaaca agttaaaaga gaaagagggg	1620
gaagtcttta cttaacaaa gcagttgaat actttgcagg atcttttgc caaagccat	1680
aaagagaaaac ttactttgc gaggaaacta aaaaca	1716

<210> SEQ ID NO 29

<211> LENGTH: 2406

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

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caagaagaac tggcagataa tttattgtt cccttatcca aggtggaaatg aaatgagctt	120
aaaagtggaaa agcaagaaaa tttgtatcac ttttcagaa ttactcagtc actaatgaaat	180
atgaaagctc aagaagtggc gctggcttgc gaagaatgtt aaaaagatgg agaagaacaa	240
gcaaaaatttgc aaaatcaattt aaaaactaaa gtaatgaaac tggaaaatgtt actggatgtt	300
gctcagcgtt ctgcagggtt acggatactt cggtttttgc gtaatgaaat ttgccaactt	360
gaaaaacaaat tagaacaacaa agatagagaa ttggaggaca tggaaaagga gttggagaaa	420
gagaagaaaatg ttaatgagca attggctttt cggaaatgaggc aggcagaaaa tgaaaacagc	480

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aaatataagaa gagagaacaa acgtctaaag aaaaagaatg aacaacttg tcaggatatt	540
attgactacc agaaacaaat agattcacag aaagaaaacac ttttatcaag aagaggggaa	600
actgaaaaca tttctcaagg agatagaata agtcaaagaa aattggattt attgagctc	660
aaaaatatga gtgaagcaca atcaaagaat gaatttcattt caagagaact aattgaaaaa	720
gaaagagatt tagaaaggag taggacagtg atagccaaat ttccagaataa attaaaagaa	780
ttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaag	840
gaaatgcaga aagatcctga tgttaaagga ggagaaacat ctctaattat ccctagcct	900
gaaaagactag ttaatgctat agaatcaaag aatgcagaag gaatcttga tgcgagtcg	960
catttgaag cccaaagttga tcagcttacc ggaagaaaatg aagaattaag acaggagctc	1020
agggaatctc ggaaagaggc tataaattat tcacagcagt tggcaaaagc taatttaag	1080
atagaccatc ttgaaaaaga aactagtctt ttacgacaat cagaaggatc gaatgttgtt	1140
tttaaaggaa ttgacttacc tgatggata gcaccatcta gtgccagttt cattaattct	1200
cagaatgaat atttaataca ttgtttacag gaactagaaa ataaagaaaa aaagttaag	1260
aattttagaag attctcttga agattacaac agaaaatttg ctgttaattcg tcatcaacaa	1320
agtttgttgt ataaagaata cctaagtgaa aaggagacct ggaaaacaga atctaaaaca	1380
ataaaaagagg aaaagagaaa acttgaggat caagtccaaac aagatgctat aaaagtaaaa	1440
gaatataata atttgctcaa tgctttcag atggattcgg atgaaatgaa aaaaactt	1500
gcagaaaata gtaggaaaat tactgttttga caagtgaatg aaaaatcaact tataaggcaa	1560
tatacaacct tagtagaatt ggagcgacaa cttagaaaag aaaaatgagaa gcaaaagaat	1620
gaattgttgtt caatggaggc tgaagttgtt gaaaaatttg ggtgtttgca aagatttaag	1680
gaaatggcca ttttcaagat tgcttcgtc caaaaatgtt tagataatag tgtttcttg	1740
tctgaactag aactggctaa taaacagtac aatgaactga ctgctaagta cagggacatc	1800
ttgcaaaaag ataatatgct tggtaaaga acaagtaact tggaaacacct ggagtgtgaa	1860
aacatctct taaaagaaca agtggagtct ataaataaag aactggagat taccaaggaa	1920
aaacttcaca ctattgaaca agcctggaa cagggaaacta aatttagttaa tgaatctagc	1980
atggataagg caaagaaaatc aataaccaac agtgacattt tttccatttc aaaaaaaaaata	2040
actatgtgg aatgaagga attaaatgaa aggcaaggccc ctgaacatgt tcaaaaaatg	2100
tatgaacact tacggacttc gttaaagcaa atggaggaac gtaattttga attggaaacc	2160
aaattttgtcg agcttaccaa aatcaatttg gatgcacaga aggtggaca gatgttaaga	2220
gatgaatttag ctgatagtgtt gagcaaggca gtaagtgtatg ctgataggca acggattcta	2280
gaatttagaga agaatgaaaat ggaactaaaa gttgaagtgtt caaaaactgag agagatttct	2340
gatattggcca gaagacaagt tgaaattttg aatgcacaac aacaatctag ggacaaggaa	2400
gtataaa	2406

<210> SEQ ID NO 30
<211> LENGTH: 1316
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Lys	Asn	Thr	Cys	Ile	Ile	Glu	Asp	Leu	Lys	Asn	Glu	Leu	Gln	Arg	Asn
1				5		10			15						

Lys	Gly	Ala	Ser	Thr	Leu	Ser	Gln	Gln	Thr	His	Met	Lys	Ile	Gln	Ser
20				25					30						

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Thr Leu Asp Ile Leu Lys Glu Lys Thr Lys Glu Ala Glu Arg Thr Ala
 35 40 45
 Glu Leu Ala Glu Ala Asp Ala Arg Glu Lys Asp Lys Glu Leu Val Glu
 50 55 60
 Ala Leu Lys Arg Leu Lys Asp Tyr Glu Ser Gly Val Tyr Gly Leu Glu
 65 70 75 80
 Asp Ala Val Val Glu Ile Lys Asn Cys Lys Asn Gln Ile Lys Ile Arg
 85 90 95
 Asp Arg Glu Ile Glu Ile Leu Thr Lys Glu Ile Asn Lys Leu Glu Leu
 100 105 110
 Lys Ile Ser Asp Phe Leu Asp Glu Asn Glu Ala Leu Arg Glu Arg Val
 115 120 125
 Gly Leu Glu Pro Lys Thr Met Ile Asp Leu Thr Glu Phe Arg Asn Ser
 130 135 140
 Lys His Leu Lys Gln Gln Tyr Arg Ala Glu Asn Gln Ile Leu Leu
 145 150 155 160
 Lys Glu Ile Glu Ser Leu Glu Glu Arg Leu Asp Leu Lys Lys Lys
 165 170 175
 Ile Arg Gln Met Ala Gln Glu Arg Gly Lys Arg Ser Ala Thr Ser Gly
 180 185 190
 Leu Thr Thr Glu Asp Leu Asn Leu Thr Glu Asn Ile Ser Gln Gly Asp
 195 200 205
 Arg Ile Ser Glu Arg Lys Leu Asp Leu Leu Ser Leu Lys Asn Met Ser
 210 215 220
 Glu Ala Gln Ser Lys Asn Glu Phe Leu Ser Arg Glu Leu Ile Glu Lys
 225 230 235 240
 Glu Arg Asp Leu Glu Arg Ser Arg Thr Val Ile Ala Lys Phe Gln Asn
 245 250 255
 Lys Leu Lys Glu Leu Val Glu Glu Asn Lys Gln Leu Glu Glu Gly Met
 260 265 270
 Lys Glu Ile Leu Gln Ala Ile Lys Glu Met Gln Lys Asp Pro Asp Val
 275 280 285
 Lys Gly Gly Glu Thr Ser Leu Ile Ile Pro Ser Leu Glu Arg Leu Val
 290 295 300
 Asn Ala Ile Glu Ser Lys Asn Ala Glu Gly Ile Phe Asp Ala Ser Leu
 305 310 315 320
 His Leu Lys Ala Gln Val Asp Gln Leu Thr Gly Arg Asn Glu Glu Leu
 325 330 335
 Arg Gln Glu Leu Arg Glu Ser Arg Lys Glu Ala Ile Asn Tyr Ser Gln
 340 345 350
 Gln Leu Ala Lys Ala Asn Leu Lys Ile Asp His Leu Glu Lys Glu Thr
 355 360 365
 Ser Leu Leu Arg Gln Ser Glu Gly Ser Asn Val Val Phe Lys Gly Ile
 370 375 380
 Asp Leu Pro Asp Gly Ile Ala Pro Ser Ser Ala Ser Ile Ile Asn Ser
 385 390 395 400
 Gln Asn Glu Tyr Leu Ile His Leu Leu Gln Glu Leu Glu Asn Lys Glu
 405 410 415
 Lys Lys Leu Lys Asn Leu Glu Asp Ser Leu Glu Asp Tyr Asn Arg Lys
 420 425 430
 Phe Ala Val Ile Arg His Gln Gln Ser Leu Leu Tyr Lys Glu Tyr Leu
 435 440 445

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Ser Glu Lys Glu Thr Trp Lys Thr Glu Ser Lys Thr Ile Lys Glu Glu
 450 455 460

Lys Arg Lys Leu Glu Asp Gln Val Gln Gln Asp Ala Ile Lys Val Lys
 465 470 475 480

Glu Tyr Asn Asn Leu Leu Asn Ala Leu Gln Met Asp Ser Asp Glu Met
 485 490 495

Lys Lys Ile Leu Ala Glu Asn Ser Arg Lys Ile Thr Val Leu Gln Val
 500 505 510

Asn Glu Lys Ser Leu Ile Arg Gln Tyr Thr Thr Leu Val Glu Leu Glu
 515 520 525

Arg Gln Leu Arg Lys Glu Asn Glu Lys Gln Lys Asn Glu Leu Leu Ser
 530 535 540

Met Glu Ala Glu Val Cys Glu Lys Ile Gly Cys Leu Gln Arg Phe Lys
 545 550 555 560

Glu Met Ala Ile Phe Lys Ile Ala Ala Leu Gln Lys Val Val Asp Asn
 565 570 575

Ser Val Ser Leu Ser Glu Leu Glu Leu Ala Asn Lys Gln Tyr Asn Glu
 580 585 590

Leu Thr Ala Lys Tyr Arg Asp Ile Leu Gln Lys Asp Asn Met Leu Val
 595 600 605

Gln Arg Thr Ser Asn Leu Glu His Leu Glu Cys Glu Asn Ile Ser Leu
 610 615 620

Lys Glu Gln Val Glu Ser Ile Asn Lys Glu Leu Glu Ile Thr Lys Glu
 625 630 635 640

Lys Leu His Thr Ile Glu Gln Ala Trp Glu Gln Glu Thr Lys Leu Gly
 645 650 655

Asn Glu Ser Ser Met Asp Lys Ala Lys Lys Ser Ile Thr Asn Ser Asp
 660 665 670

Ile Val Ser Ile Ser Lys Lys Ile Thr Met Leu Glu Met Lys Glu Leu
 675 680 685

Asn Glu Arg Gln Arg Ala Glu His Cys Gln Lys Met Tyr Glu His Leu
 690 695 700

Arg Thr Ser Leu Lys Gln Met Glu Glu Arg Asn Phe Glu Leu Glu Thr
 705 710 715 720

Lys Phe Ala Glu Leu Thr Lys Ile Asn Leu Asp Ala Gln Lys Val Glu
 725 730 735

Gln Met Leu Arg Asp Glu Leu Ala Asp Ser Val Ser Lys Ala Val Ser
 740 745 750

Asp Ala Asp Arg Gln Arg Ile Leu Glu Leu Glu Lys Asn Glu Met Glu
 755 760 765

Leu Lys Val Glu Val Ser Lys Leu Arg Glu Ile Ser Asp Ile Ala Arg
 770 775 780

Arg Gln Val Glu Ile Leu Asn Ala Gln Gln Ser Arg Asp Lys Glu
 785 790 795 800

Val Glu Ser Leu Arg Met Gln Leu Leu Asp Tyr Gln Ala Gln Ser Asp
 805 810 815

Glu Lys Ser Leu Ile Ala Lys Leu His Gln His Asn Val Ser Leu Gln
 820 825 830

Leu Ser Glu Ala Thr Ala Leu Gly Lys Leu Glu Ser Ile Thr Ser Lys
 835 840 845

Leu Gln Lys Met Glu Ala Tyr Asn Leu Arg Leu Glu Gln Lys Leu Asp
 850 855 860

Glu Lys Glu Gln Ala Leu Tyr Tyr Ala Arg Leu Glu Gly Arg Asn Arg

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865	870	875	880
Ala Lys His Leu Arg Gln Thr Ile Gln Ser Leu Arg Arg Gln Phe Ser			
885	890	895	
Gly Ala Leu Pro Leu Ala Gln Gln Glu Lys Phe Ser Lys Thr Met Ile			
900	905	910	
Gln Leu Gln Asn Asp Lys Leu Lys Ile Met Gln Glu Met Lys Asn Ser			
915	920	925	
Gln Gln Glu His Arg Asn Met Glu Asn Lys Thr Leu Glu Met Glu Leu			
930	935	940	
Lys Leu Lys Gly Leu Glu Glu Leu Ile Ser Thr Leu Lys Asp Thr Lys			
945	950	955	960
Gly Ala Gln Lys Val Ile Asn Trp His Met Lys Ile Glu Glu Leu Arg			
965	970	975	
Leu Gln Glu Leu Lys Leu Asn Arg Glu Leu Val Lys Asp Lys Glu Glu			
980	985	990	
Ile Lys Tyr Leu Asn Asn Ile Ile Ser Glu Tyr Glu Arg Thr Ile Ser			
995	1000	1005	
Ser Leu Glu Glu Ile Val Gln Gln Asn Lys Phe His Glu Glu			
1010	1015	1020	
Arg Gln Met Ala Trp Asp Gln Arg Glu Val Asp Leu Glu Arg Gln			
1025	1030	1035	
Leu Asp Ile Phe Asp Arg Gln Gln Asn Glu Ile Leu Asn Ala Ala			
1040	1045	1050	
Gln Lys Phe Glu Glu Ala Thr Gly Ser Ile Pro Asp Pro Ser Leu			
1055	1060	1065	
Pro Leu Pro Asn Gln Leu Glu Ile Ala Leu Arg Lys Ile Lys Glu			
1070	1075	1080	
Asn Ile Arg Ile Ile Leu Glu Thr Arg Ala Thr Cys Lys Ser Leu			
1085	1090	1095	
Glu Glu Lys Leu Lys Glu Lys Glu Ser Ala Leu Arg Leu Ala Glu			
1100	1105	1110	
Gln Asn Ile Leu Ser Arg Asp Lys Val Ile Asn Glu Leu Arg Leu			
1115	1120	1125	
Arg Leu Pro Ala Thr Ala Glu Arg Glu Lys Leu Ile Ala Glu Leu			
1130	1135	1140	
Gly Arg Lys Glu Met Glu Pro Lys Ser His His Thr Leu Lys Ile			
1145	1150	1155	
Ala His Gln Thr Ile Ala Asn Met Gln Ala Arg Leu Asn Gln Lys			
1160	1165	1170	
Glu Glu Val Leu Lys Lys Tyr Gln Arg Leu Leu Glu Lys Ala Arg			
1175	1180	1185	
Glu Glu Gln Arg Glu Ile Val Lys Lys His Glu Glu Asp Leu His			
1190	1195	1200	
Ile Leu His His Arg Leu Glu Leu Gln Ala Asp Ser Ser Leu Asn			
1205	1210	1215	
Lys Phe Lys Gln Thr Ala Trp Asp Leu Met Lys Gln Ser Pro Thr			
1220	1225	1230	
Pro Val Pro Thr Asn Lys His Phe Ile Arg Leu Ala Glu Met Glu			
1235	1240	1245	
Gln Thr Val Ala Glu Gln Asp Asp Ser Leu Ser Ser Leu Leu Val			
1250	1255	1260	
Lys Leu Lys Lys Val Ser Gln Asp Leu Glu Arg Gln Arg Glu Ile			
1265	1270	1275	

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Thr	Glu	Leu	Lys	Val	Lys	Glu	Phe	Glu	Asn	Ile	Lys	Leu	Gln	Leu
1280						1285						1290		
Gln	Glu	Asn	His	Glu	Asp	Glu	Val	Lys	Lys	Val	Lys	Ala	Glu	Val
1295						1300						1305		
Glu	Asp	Leu	Lys	Tyr	Leu	Leu	Asp							
1310						1315								

<210> SEQ ID NO 31
<211> LENGTH: 514
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 31

Thr	Thr	Gly	Met	Thr	Val	Asp	Gln	Val	Leu	Gly	Ile	Arg	Ala	Leu	Glu
1								5			10			15	
Ser	Glu	Lys	Glu	Leu	Glu	Glu	Leu	Lys	Lys	Arg	Asn	Leu	Asp	Leu	Glu
	20							25			30				
Asn	Asp	Ile	Leu	Tyr	Met	Arg	Ala	His	Gln	Ala	Leu	Pro	Arg	Asp	Ser
	35							40			45				
Val	Val	Glu	Asp	Leu	His	Leu	Gln	Asn	Arg	Tyr	Leu	Gln	Glu	Lys	Leu
	50							55			60				
His	Ala	Leu	Glu	Lys	Gln	Phe	Ser	Lys	Asp	Thr	Tyr	Ser	Lys	Pro	Ser
	65							70			75			80	
Ile	Ser	Gly	Ile	Glu	Ser	Asp	Asp	His	Cys	Gln	Arg	Glu	Gln	Glu	Leu
	85							90			95				
Gln	Lys	Glu	Asn	Leu	Lys	Leu	Ser	Ser	Glu	Asn	Ile	Glu	Leu	Lys	Phe
	100							105			110				
Gln	Leu	Glu	Gln	Ala	Asn	Lys	Asp	Leu	Pro	Arg	Leu	Lys	Asn	Gln	Val
	115							120			125				
Arg	Asp	Leu	Lys	Glu	Met	Cys	Glu	Phe	Leu	Lys	Lys	Glu	Lys	Ala	Glu
	130							135			140				
Val	Gln	Arg	Lys	Leu	Gly	His	Val	Arg	Gly	Ser	Gly	Arg	Ser	Gly	Lys
	145							150			155			160	
Thr	Ile	Pro	Glu	Leu	Glu	Lys	Thr	Ile	Gly	Leu	Met	Lys	Lys	Val	Val
	165							170			175				
Glu	Lys	Val	Gln	Arg	Glu	Asn	Glu	Gln	Leu	Lys	Lys	Ala	Ser	Gly	Ile
	180							185			190				
Leu	Thr	Ser	Glu	Lys	Met	Ala	Asn	Ile	Glu	Gln	Glu	Asn	Glu	Lys	Leu
	195							200			205				
Lys	Ala	Glu	Leu	Glu	Lys	Leu	Lys	Ala	His	Leu	Gly	His	Gln	Leu	Ser
	210							215			220				
Met	His	Tyr	Glu	Ser	Lys	Thr	Lys	Gly	Thr	Glu	Lys	Ile	Ile	Ala	Glu
	225							230			235			240	
Asn	Glu	Arg	Leu	Arg	Lys	Glu	Leu	Lys	Glu	Thr	Asp	Ala	Ala	Glu	
	245							250			255				
Lys	Leu	Arg	Ile	Ala	Lys	Asn	Asn	Leu	Glu	Ile	Leu	Asn	Glu	Lys	Met
	260							265			270				
Thr	Val	Gln	Leu	Glu	Glu	Thr	Gly	Lys	Arg	Leu	Gln	Phe	Ala	Glu	Ser
	275							280			285				
Arg	Gly	Pro	Gln	Leu	Glu	Gly	Ala	Asp	Ser	Lys	Ser	Trp	Lys	Ser	Ile
	290							295			300				
Val	Val	Thr	Arg	Met	Tyr	Glu	Thr	Lys	Leu	Lys	Glu	Leu	Glu	Thr	Asp
	305							310			315			320	
Ile	Ala	Lys	Lys	Asn	Gln	Ser	Ile	Thr	Asp	Leu	Lys	Gln	Leu	Val	Lys

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325	330	335
Glu Ala Thr Glu Arg Glu Gln Lys Val Asn Lys Tyr Asn Glu Asp Leu		
340	345	350
Glu Gln Gln Ile Lys Ile Leu Lys His Val Pro Glu Gly Ala Glu Thr		
355	360	365
Glu Gln Gly Leu Lys Arg Glu Leu Gln Val Leu Arg Leu Ala Asn His		
370	375	380
Gln Leu Asp Lys Glu Lys Ala Glu Leu Ile His Gln Ile Glu Ala Asn		
385	390	395
Lys Asp Gln Ser Gly Ala Glu Ser Thr Ile Pro Asp Ala Asp Gln Leu		
405	410	415
Lys Glu Lys Ile Lys Asp Leu Glu Thr Gln Leu Lys Met Ser Asp Leu		
420	425	430
Glu Lys Gln His Leu Lys Glu Glu Ile Lys Lys Leu Lys Lys Glu Leu		
435	440	445
Glu Asn Phe Asp Pro Ser Phe Phe Glu Glu Ile Glu Asp Leu Lys Tyr		
450	455	460
Asn Tyr Lys Glu Glu Val Lys Lys Asn Ile Leu Leu Glu Glu Lys Val		
465	470	475
Lys Lys Leu Ser Glu Gln Leu Gly Val Glu Leu Thr Ser Pro Val Ala		
485	490	495
Ala Ser Glu Glu Phe Glu Asp Glu Glu Ser Pro Val Asn Phe Pro		
500	505	510

Ile Tyr

<210> SEQ ID NO 32
 <211> LENGTH: 1545
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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acaactggca tgactgttga tcaggttttg ggaatacggag ctttggagtc agaaaaagaa      60
ttggaagaat taaaaaaagag aaatcttgac tttagaaaatg atatatttta tatggggcc      120
caccaagctc ttccctcgaga ttctgttgc taagatttac atttacaaaa tagataacctc      180
caagaaaaac ttcatgtctt agaaaaacag ttttcaaagg atacatatcc taagecttca      240
atttcaggaa tagagtcaga tgatcattgt cagagagaac aggagcttca gaaggaaaac      300
ttgaagtgt catctgaaaa tattgaactg aaatttcagc ttgaacaagc aaataaagat      360
ttgccaagat taaagaatca agtcagagat ttgaaggaaa tgtgtgaatt tcttaagaaa      420
aaaaaaaggc aagttcagcg gaaacttggc catgttagag ggtctggtag aagtggaaag      480
acaatcccag aactggaaaa aaccatttgtt ttaatgaaaa aagttagttga aaaagtccag      540
agagaaaaatg aacagttgaa aaaagcatca ggaatattga ctatgtaaaa aatggctaat      600
attgagcagg aaaaatgaaaa attgaaggct gaatttagaaa aactttaaagc tcatcttggg      660
catcagttga gcatgcacta tgaatccaag accaaaggca cagaaaaat tattgtcttga      720
aatgaaaggc ttctgttgc actttaaaaaa gaaactgtatg ctgcagagaa attacggata      780
gcaaaagaata atttagagat attaaatgaa aagatgacag ttcaactaga agagactgg      840
aagagattgc agtttgcaga aagcagaggt ccacagcttg aaggtgctga cagtaagagc      900
tggaaatcca ttgtggttac aagaatgtat gaaaccaagt taaaagaatt ggaaaactgat      960
attgccccaaa aaaatcaaag cattactgac cttaaacagc ttgtaaaaga agcaacagag      1020

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agagaacaaa aagttaacaa atacaatgaa gaccttgaac aacagattaa gattcttaaa	1080
catgttcctg aagggtgctga gacagagcaa ggcccttaaac gggagctca agttcttaga	1140
ttagctaatac atcagctgga taaagagaaa gcagaattaa tccatcagat agaagctaac	1200
aaggacaaa gtggagctga aagcaccata cctgatgctg atcaactaaa ggaaaaaata	1260
aaagatctag agacacagct caaatgtca gatctagaaa agcagcattt gaaggaggaa	1320
ataaagaagc tgaaaaaaga actggaaaat ttgtatcctt catttttga agaaattgaa	1380
gatcttaagt ataattacaa ggaagaagtg aagaagaata ttctcttaga agagaaggt	1440
aaaaaaaaactt cagaacaatt gggagttgaa ttaactagcc ctgttgctgc ttctgaagag	1500
tttgaagatg aagaagaaag tcctgttaat ttccccattt actaa	1545

<210> SEQ ID NO 33

<211> LENGTH: 3948

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

aagaataactt gtattattga agatttgaaa aatgagctcc aaagaaaacaa aggtgcttca	60
accctttctc aacagactca tatgaaaatt cagtcaacgt tagacatttt aaaagagaaa	120
actaaagagg ctgagagaac agctgaactg gctgaggctg atgctaggga aaaggataaa	180
gaatttagttg aggctctgaa gaggttaaaa gattatgaat cgggagttata tggtttagaa	240
gtatgtgtcg ttgaaataaa gaattgtaaa aaccaaattt aaataagaga tcgagagatt	300
gaaatattaa caaaggaaat caataaaactt gaattgaaga tcagtgattt ccttgatgaa	360
aatgaggcac ttagagagcg tggggccctt gaaccaaaga caatgatttga tttaactgaa	420
tttagaaata gcaaacactt aaaacagcg cagtagacag cttgaaaacca gatttttg	480
aaagagattt gaaatctaga ggaagaacga ctgtatctgaa aaaaaaaaaat tcgtcaatg	540
gctcaagaaa gagggaaaag aagtgcact tcaggattaa ccactgagga cctgaaccta	600
actgaaaaca tttctcaagg agatagaata agtgaagaaa aattggattt attgagcctc	660
aaaaatatgaa gtgaagcaca atcaaagaat gaatttttttta caagagaact aattgaaaaa	720
gaaaagagatt tagaaaggag taggacagtg atagccaaat ttccaaataa attaaaagaa	780
tttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaag	840
gaaatgcaga aagatcctgaa tggtaaaagga ggagaaacat ctctaaattat ccctagcctt	900
gaaaagacttag ttaatgttat agaatcaaag aatgcagaag gaatcttgc tgccgatctg	960
catttggaaag cccaaatgtca tcagcttacc ggaagaaaatg aagaattaag acaggagctc	1020
agggaatctc ggaaagaggc tataaattat tcacagcgt tggcaaaagc taattaaag	1080
atagaccatc ttgaaaaaga aacttgtctt ttacgacaat cagaaggatc gaatgttgc	1140
tttaaaggaa ttgacttacc tggatggata gcaccatcta gtgccagtat cattaattct	1200
cagaatgaat atttaataca ttgttacag gaacttagaaa ataaagaaaa aaagttaag	1260
aattttagaaat ttctcttgc agattacaac agaaaatttg ctgtatctg tcatcaacaa	1320
agtttggatg ataaagaata cctaaatgtgaa aaggagacct ggaaaacaga atctaaaaca	1380
ataaaagagg aaaagagaaa acttgaggat caagtccaaac aagatgctat aaaagtaaaa	1440
gaatataata atttgcctaa tgcttccatc atggattcgg atgaaatgaa aaaaatactt	1500
gcagaaaata gtagggaaaat tactgttttgc caagtgaatg aaaaatcact tataaggca	1560
tataacaacct tagtagaatt ggagcgcacaa ctttagaaaag aaaatgagaa gcaaaagaat	1620

gaaattgttgt caatggaggc tgaagttgt gaaaaaattt ggtgttgca aagatttaag 1680
 gaaaatggcca ttttcaagat tgcaagtc tccaaaggatg tagataatag tgtttcttg 1740
 tctgaactag aactggctaa taaacagtac aatgaactga ctgctaagta cagggacatc 1800
 ttgcaaaaag ataatatgct tggtaaaga acaagtaact tggaaacacct ggagtgtgaa 1860
 aacatctctt taaaagaaca agtggagtct ataaataaag aactggagat taccaaggaa 1920
 aaacttcaca ctattgaaca agcctggaa caggaaacta aatttagtta tgaatctgc 1980
 atggataagg caaagaaatc aataaccaac agtgacattt tttccattt aaaaaaaata 2040
 actatgtgg aatgtggaa attaaatgaa aggcagcggg ctgaacatg tcaaaaaatg 2100
 tatgaacact tacggacttc gttaaagcaa atggaggaac gtaattttga attggaaacc 2160
 aaatttgctg agcttaccaa aatcaattt gatgcacaga aggtggaaaca gatgttaaga 2220
 gatgaattag ctgatagtgt gagcaaggca gtaagtgtatg ctgataggca acggattcta 2280
 gaatttagaga agaatgaaat ggaactaaaa gttgaagtgt caaaactgag agagattct 2340
 gatattgcca gaagacaagt tgaaatttt gatgcacaac aacaatctg ggacaaggaa 2400
 gtagagtccc tcagaatgca actgtogac tatcaggcc acgtctgtatg aaagtgcgtc 2460
 attgccaagt tgccaccaaca taatgtctt ctcaactgta gtgaggotac tgcttttgt 2520
 aagttggagt caatttacatc taaactgcag aagatggagg cctacaactt gcgccttagag 2580
 cagaaaactt atgaaaaaga acaggctctc tattatgctc gtttggaggg aagaaacaga 2640
 gcaaaacatc tgcgcacaaac aatttgcgtct ctacgacgac agtttagtgg agctttaccc 2700
 ttggcacaac aggaaaagtt ctccaaaaca atgattcaac tacaatgaa caaacttaag 2760
 ataatgcaag aatgaaaaaa ttctcaacaa gaacatgaa atatggagaa caaaacattt 2820
 gagatggaat taaaattaaa gggcctggaa gagttataa gcactttaaa ggataccaaa 2880
 ggagccccaa aggtatcaa ctggcatatg aaaatagaag aacttcgtct tcaagaactt 2940
 aaactaaatc gggaaattgtt caaggataaa gaagaaataa aatatttggaa taacataatt 3000
 tctgaatatg aacgtacaat cagcgtctt gaagaagaaa ttgtgcacaaca gaacaagttt 3060
 catgaagaaa gacaaatggc ctggatcaa agagaagttt acctggaaacg ccaactagac 3120
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 ggatcaatcc ctgaccctag tttgcccctt ccaaatcaac ttgagatcgc tctaaggaaa 3240
 attaaggaga acattcgaat aattcttagaa acacggggcaatc ctgcataactt actagaagag 3300
 aaactaaaag agaaagaatc tgctttaaagg ttagcagaac aaaatataact gtcaagagac 3360
 aaagtaatca atgaaactgag gcttcgattt cctgccactg cagaaagaga aaagctcata 3420
 gctgagatgtt gcaaaaaaaa gatggaaacca aatcttcacc acacattt gaaatgttcat 3480
 caaacatttgc caaacatgca agcaaggat aatcaaaaag aagaagtattt aaagaagtat 3540
 caacgtcttc tagaaaaagc cagagaggag caaagagaaa ttgtgaagaa acatgaggaa 3600
 gacccatca ttcttcatca cagattt gatggccatc atagtttactt aaataaaattt 3660
 aaacaaacgg cttgggatttt aatgtggaaac tctccactc cagtttcttccatca caacaaggat 3720
 ttatcgatc tggctgagat ggaacagaca gtagcagaac aagatgactc tctttccatca 3780
 ctcttggatca aactaaagaa agtacatcataa gatttggaga gacaaagaga aatctactgaa 3840
 ttaaaaagttaa aagaatttga aatataatcaaa ttacagcttc aagaaaacca tgaagatgaa 3900
 gtgaaaaaaag taaaagcggg aatgtggat ttaaagtatc ttctggac 3948

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-continued

<210> SEQ ID NO 34
<211> LENGTH: 2406
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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caagaagaac tggcagataa ttatttgatt tccttatcca aggtggaaat aaatgagcta	120
aaaagtgaaa agcaagaaaa tgtgatacac ctttcgaaa ttactcagtc actaatgaag	180
atgaaagctc aagaagtggc gctggcttgc gaagaagtag aaaaagctgg agaagaacaa	240
gc当地atggaaaatccattt aaaaactaaa gtaatgaaac tggaaaatga actggagatg	300
gctcagcagt ctgcagggtgg acgagatact cggttttac gtaatgaaat ttgccaactt	360
gaaaaacaat tagaacaat agatagagaa ttggaggaca tggaaaagga gttggagaaa	420
gagaagaaag ttaatgagca attggcttctt cgaaatgagg aggcagaaaa tgaaaacagc	480
aaatttaaagaa gagagaacaa acgtctaaag aaaaagaatg aacaacttttgc tcaggatatt	540
attgactacc agaaacaaat agattcacag aaagaaacac ttttatcaag aagagggaa	600
actgaaaaca ttctcaagg agatagaata agtggaaagaa aattggattt attgagcctc	660
aaaaatatga gtgaagcaca atcaaagaat gaatttctt caagagaact aattgaaaaa	720
gaaagagatt tagaaaggag taggacagtg atagccaaat ttcagaataa attaaagaa	780
ttagttgaag aaaataagca acttgaagaa ggtatgaaag aaatattgca agcaattaa	840
gaaaatgcaga aagatcctga tggtaaaagga ggagaaacat ctctaattat ccctagcctt	900
gaaagactag ttaatgctat agaatcaaag aatgcagaag gaatcttgc tgcgagtctg	960
catttggaaag cccaaatgtca tcagttacc ggaagaaatg aagaattaag acaggagctc	1020
aggaaatctc ggaaagaggc tataaattat tcacagcgt tggccaaaagc taattaaag	1080
atagaccatc ttgaaaaga aactagtctt ttacgacaat cagaaggatc gaatgttgtt	1140
tttaaaggaa ttgacttacc tggatggata gcaccatcta gtgccagtat cattaattct	1200
cagaatgaat atttaataca tttgttacag gaactagaaaa ataaagaaaa aaagttaaag	1260
aatttagaaat ttctcttgc agattacaac agaaaatttg ctgttaattcg tcataccaa	1320
agtttggatg ataaagaata cctaaatgtaa aaggagacat ggaaaacaga atctaaaaca	1380
ataaaagagg aaaagagaaaa acttgaggat caagtccaaac aagatgctat aaaagtaaaa	1440
gaatataata atttgcctaa tgcttttcag atggattcgg atgaaatgaa aaaaatactt	1500
gcagaaaata gtagaaaaat tactgttttgc caagtgaatg aaaaatcact tataaggcaa	1560
tataacaacct tagttagaatt ggagcgacaa cttgaaaaag aaaaatgagaa gcaaaagaat	1620
gaattgttgtt caatggaggc tgaagttgtt gaaaaatttg ggtgtttgc aagatttaag	1680
gaaatggccca tttcaagat tgccagcttc caaaaatgtt tagataatag tggatgttttgc	1740
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ttgcaaaaatg ataataatgct tggtaaaaga acaagtaact tggaaacacct ggagtgtgaa	1860
aacatctcct taaaagaaca agtggagtct ataataaaag aactggagat tccaaggaa	1920
aaacttcaca ctattgaaca agcctggaa cagggaaacta aatttagttaa tgaatctac	1980
atggataagg caaagaaatc aataaccaac agtgcacattt tttccatttc aaaaaaataa	2040
actatgctgg aatgaagga attaaatgaa aggccggcggg ctgaacatg tcaaaaaatg	2100
atgaaacact tacggacttc gttaaagcaa atggaggaaac gtaatgttgc attggaaacc	2160

aaatggctg agcttaccaa aatcaatttg gatgcacaga aggtggaca gatgttaaga	2220
gtgaatttag ctgatagtgt gagcaaggca gtaagtatgt ctgataggca acggattcta	2280
gaatttagaga agaatgaaat ggaactaaaa gttgaatgt caaaaactgag agagattct	2340
gatattgcca gaagacaagt tgaaaatttg aatgcacaac aacaatctag ggacaaggaa	2400
gtataa	2406

<210> SEQ ID NO 35

<211> LENGTH: 2946

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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caggaagaac tggctgacaa cctgctgatc agectgtcca aggtggaaat gaatgagctg	120
aagtctgaga agcaggagaa cgtatccac ctgttcagaa tcacccagag cctgtatgaa	180
atgaaggcac aggagggtgga gctggccctg gaggagggtgg agaaggcagg agaggagcag	240
gccaagttcg agaatcagct gaagaccaaa gtatgaaatc tggagaacga gctggagatg	300
gcacagcagt cccggggagg caggataca cgcttctgc ggaacgagat ctgccagctg	360
gagaagcgc tggagcagaa ggacaggag ctggaggata tggagaagga gctggagaag	420
gagaagaagg tgaacgagca gctggccctg cgcaatgagg aggccgagaa tgagaatagc	480
aagctgcccggagaaacaa gcccgtgaag aagaagaacg agcagctgtg ccaggacatc	540
atcgattacc agaagcagat cgactcccac aaggagacac tgctgagcag gagggggag	600
gactccgatt atcgccggca gctgtccaag aagaattacg agctgatcca gtatctggat	660
gagatccaga ccctgacaga gccaacgag aagatcgagg tgcagaacca ggagatgaga	720
aagaatctgg aggagtcgt gcaggagatg gagaagatg cccgacgatca caacaggatg	780
aaggccatcg tgcaccagac agacaatgtg atcgatcgc tgaagaagga gaacgacac	840
tatcagctgc aggtgcagga gctgaccatc ctgatgttgc acaagaatga ggaggacat	900
cccatcatgg tggccgtgaa cgccaaagggtg gaggagtgaa agctgatcct gagctccaag	960
gacgatgaga tcatcgatgc ccaggatgc ctgcacaacc tgcgcgagaa gctgaagaat	1020
gcccagctgg acggcgataa gagcaatgtg atggcactgc agcaggaaat ccaggagagg	1080
gactcccaga tcaagatgtc gaccgagcag gtggagcagt ataccaagga gatggagaag	1140
acagagaaca tctctcaggcg acacagaatc agcgagagga agctggatct gctgtccctg	1200
aagaacatgt ccgaggccca gtctaagaat gagttcctgt cccgcgagct gatcgagaag	1260
gagcgggacc tggagcggag ccggacagtgc atcgccaaatg ttcaagaatgg gctgaaggag	1320
ctgggtggagg agaacaagca gctggaggag ggcataagg agatcctgca ggcctcaag	1380
gagatgcaga aggacccaga tgtgaaggcg ggcgagacaa gcctgatcat cccctctcg	1440
gagcgcctgg tgaacgcccattcgacatcgacaaatgcggagg gcatcttgc cgcctccctg	1500
cacccatgttgc cccagggtggaa tcagatgcata ggcgcataatgc aggcgtgcg gcaaggagctg	1560
agagagtcata ggaaggaggc catcaattac agccagcagc tggccaaaggc caacctgaa	1620
atcgaccacc tggagaagga gacaaggctgc ctggccgcgt ctgaggcgcg caacgtgt	1680
ttcaaggggaa tcgacccgtcc agatggaaatc gcaacccatcgatcatc catcaactcc	1740
cagaatgagt acctgatcca cctgctgcag gagctggaga acaaggagaa gaagctgaa	1800

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aactctggagg	actctctggaa	ggattataat	agaaaaggttt	cgcgtatcatcg	gcaccacgacg	1860
tccctgtgt	acaaggagta	tctgtcttag	aaggagacat	ggaagacaga	gagcaagacc	1920
atcaaggagg	agaagaggaa	gctggaggac	caggtgcagc	aggatccat	caaggatgtaa	1980
gagtacaaca	atctgtgaa	cgcctgcag	atggactctg	atgagatgaa	gaagatcctg	2040
gccgagaata	gcagaaagat	cacagtgtct	cagggtaaacg	agaagtcct	gatcaggcag	2100
tataccacac	tggtggagct	ggagcccaag	ctggaaagg	agaacgagaa	gcagaagaat	2160
gagctgtgt	ctatggagc	cgaggtgtgc	gagaagatcg	gctgtctgca	gagattcaag	2220
gagatggcca	tctttaagat	cgcgcctctg	cagaaggatgg	tggacaattc	tgtgagcctg	2280
tccgagctgg	agctggccaa	caagcagtagc	aatgagctga	ccgccaagta	tcgcgacatc	2340
ctgcagaagg	ataacatgct	ggtgtcagcgg	acaagcaatc	tggagcacct	ggagtgcgag	2400
aacatcagcc	tgaaggagca	ggtgtggatcc	atcaacaagg	agctggagat	caccaaggag	2460
aagctgcaca	caatcgagca	ggcctgggag	caggagacaa	agctggccaa	tgagtcctct	2520
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acaatgtgg	agatgaagga	gctgaatgag	aggcagcgcg	cgcgcactg	tcagaagatg	2640
tacgagcacc	tgagaacatc	cctgaagcag	atggaggaga	ggaatttgcg	gctggagaca	2700
aagtttgcgg	agctgacaaa	gatcaacctg	gacgcccaga	aggtggagca	gatgtgtgaa	2760
gacgagctgg	ccgattccgt	gtctaaggcc	gtgagcgcag	cgcgcggca	gagaatcctg	2820
gagctggaga	agaacgagat	ggagctgaaag	gtggaggatgt	ccaagctgag	ggagatctct	2880
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gtctgt						2946

<210> SEQ ID NO 36
<211> LENGTH: 981
<212> TYPE: PRT
<213> ORGANISM: *Homo sapiens*

<400> SEQUENCE: 36

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1						5				10					15

Asp Leu Pro Arg Gln Glu Glu Leu Ala Asp Asn Leu Leu Ile Ser Leu
20 25 30

Ser Lys Val Glu Val Asn Glu Leu Lys Ser Glu Lys Gln Glu Asn Val
35 40 45

Ile His Leu Phe Arg Ile Thr Gln Ser Leu Met Lys Met Lys Ala Gln
50 55 60

Glu Val Glu Leu Ala Leu Glu Glu Val Glu Lys Ala Gly Glu Glu Gln
65 70 75 80

Ala Lys Phe Glu Asn Gln Leu Lys Thr Lys Val Met Lys Leu Glu Asn
85 90 95

Glu Leu Glu Met Ala Gin Gin Ser Ala Gly Gly Arg Asp Thr Arg Phe
100 105 110

Leu Arg Asn Glu Ile Cys Gln Leu Glu Lys Gln Leu Glu Gln Lys Asp
115 120 125

Arg Glu L^eu Glu Asp Met Glu Lys Glu L^eu Glu Lys Glu Lys Lys Val
130 135 140

Asn Glu Gln Leu Ala Leu Arg Asn Glu Glu Ala Glu Asn Glu Asn Ser
145 150 155 160

Lys Leu Arg Arg Glu Asn Lys Arg Leu Lys Lys Lys Asn Glu Gln Leu

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165	170	175
Cys Gln Asp Ile Ile Asp Tyr Gln Lys Gln Ile Asp Ser Gln Lys Glu		
180	185	190
Thr Leu Leu Ser Arg Arg Gly Glu Asp Ser Asp Tyr Arg Ser Gln Leu		
195	200	205
Ser Lys Lys Asn Tyr Glu Leu Ile Gln Tyr Leu Asp Glu Ile Gln Thr		
210	215	220
Leu Thr Glu Ala Asn Glu Lys Ile Glu Val Gln Asn Gln Glu Met Arg		
225	230	235
Lys Asn Leu Glu Glu Ser Val Gln Glu Met Glu Lys Met Thr Asp Glu		
245	250	255
Tyr Asn Arg Met Lys Ala Ile Val His Gln Thr Asp Asn Val Ile Asp		
260	265	270
Gln Leu Lys Lys Glu Asn Asp His Tyr Gln Leu Gln Val Gln Glu Leu		
275	280	285
Thr Asp Leu Leu Lys Ser Lys Asn Glu Glu Asp Asp Pro Ile Met Val		
290	295	300
Ala Val Asn Ala Lys Val Glu Glu Trp Lys Leu Ile Leu Ser Ser Lys		
305	310	315
Asp Asp Glu Ile Ile Glu Tyr Gln Gln Met Leu His Asn Leu Arg Glu		
325	330	335
Lys Leu Lys Asn Ala Gln Leu Asp Ala Asp Lys Ser Asn Val Met Ala		
340	345	350
Leu Gln Gln Gly Ile Gln Glu Arg Asp Ser Gln Ile Lys Met Leu Thr		
355	360	365
Glu Gln Val Glu Gln Tyr Thr Lys Glu Met Glu Lys Thr Glu Asn Ile		
370	375	380
Ser Gln Gly Asp Arg Ile Ser Glu Arg Lys Leu Asp Leu Leu Ser Leu		
385	390	395
Lys Asn Met Ser Glu Ala Gln Ser Lys Asn Glu Phe Leu Ser Arg Glu		
405	410	415
Leu Ile Glu Lys Glu Arg Asp Leu Glu Arg Ser Arg Thr Val Ile Ala		
420	425	430
Lys Phe Gln Asn Lys Leu Lys Glu Leu Val Glu Glu Asn Lys Gln Leu		
435	440	445
Glu Glu Gly Met Lys Glu Ile Leu Gln Ala Ile Lys Glu Met Gln Lys		
450	455	460
Asp Pro Asp Val Lys Gly Glu Thr Ser Leu Ile Ile Pro Ser Leu		
465	470	475
Glu Arg Leu Val Asn Ala Ile Glu Ser Lys Asn Ala Glu Gly Ile Phe		
485	490	495
Asp Ala Ser Leu His Leu Lys Ala Gln Val Asp Gln Leu Thr Gly Arg		
500	505	510
Asn Glu Glu Leu Arg Gln Glu Leu Arg Glu Ser Arg Lys Glu Ala Ile		
515	520	525
Asn Tyr Ser Gln Gln Leu Ala Lys Ala Asn Leu Lys Ile Asp His Leu		
530	535	540
Glu Lys Glu Thr Ser Leu Leu Arg Gln Ser Glu Gly Ser Asn Val Val		
545	550	555
Phe Lys Gly Ile Asp Leu Pro Asp Gly Ile Ala Pro Ser Ser Ala Ser		
565	570	575
Ile Ile Asn Ser Gln Asn Glu Tyr Leu Ile His Leu Leu Gln Glu Leu		
580	585	590

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Glu Asn Lys Glu Lys Lys Leu Lys Asn Leu Glu Asp Ser Leu Glu Asp
 595 600 605
 Tyr Asn Arg Lys Phe Ala Val Ile Arg His Gln Gln Ser Leu Leu Tyr
 610 615 620
 Lys Glu Tyr Leu Ser Glu Lys Glu Thr Trp Lys Thr Glu Ser Lys Thr
 625 630 635 640
 Ile Lys Glu Glu Lys Arg Lys Leu Glu Asp Gln Val Gln Gln Asp Ala
 645 650 655
 Ile Lys Val Lys Glu Tyr Asn Asn Leu Leu Asn Ala Leu Gln Met Asp
 660 665 670
 Ser Asp Glu Met Lys Lys Ile Leu Ala Glu Asn Ser Arg Lys Ile Thr
 675 680 685
 Val Leu Gln Val Asn Glu Lys Ser Leu Ile Arg Gln Tyr Thr Thr Leu
 690 695 700
 Val Glu Leu Glu Arg Gln Leu Arg Lys Glu Asn Glu Lys Gln Lys Asn
 705 710 715 720
 Glu Leu Leu Ser Met Glu Ala Glu Val Cys Glu Lys Ile Gly Cys Leu
 725 730 735
 Gln Arg Phe Lys Glu Met Ala Ile Phe Lys Ile Ala Ala Leu Gln Lys
 740 745 750
 Val Val Asp Asn Ser Val Ser Leu Ser Glu Leu Glu Leu Ala Asn Lys
 755 760 765
 Gln Tyr Asn Glu Leu Thr Ala Lys Tyr Arg Asp Ile Leu Gln Lys Asp
 770 775 780
 Asn Met Leu Val Gln Arg Thr Ser Asn Leu Glu His Leu Glu Cys Glu
 785 790 795 800
 Asn Ile Ser Leu Lys Glu Gln Val Glu Ser Ile Asn Lys Glu Leu Glu
 805 810 815
 Ile Thr Lys Glu Lys Leu His Thr Ile Glu Gln Ala Trp Glu Gln Glu
 820 825 830
 Thr Lys Leu Gly Asn Glu Ser Ser Met Asp Lys Ala Lys Lys Ser Ile
 835 840 845
 Thr Asn Ser Asp Ile Val Ser Ile Ser Lys Lys Ile Thr Met Leu Glu
 850 855 860
 Met Lys Glu Leu Asn Glu Arg Gln Arg Ala Glu His Cys Gln Lys Met
 865 870 875 880
 Tyr Glu His Leu Arg Thr Ser Leu Lys Gln Met Glu Glu Arg Asn Phe
 885 890 895
 Glu Leu Glu Thr Lys Phe Ala Glu Leu Thr Lys Ile Asn Leu Asp Ala
 900 905 910
 Gln Lys Val Glu Gln Met Leu Arg Asp Glu Leu Ala Asp Ser Val Ser
 915 920 925
 Lys Ala Val Ser Asp Ala Asp Arg Gln Arg Ile Leu Glu Leu Glu Lys
 930 935 940
 Asn Glu Met Glu Leu Lys Val Glu Val Ser Lys Leu Arg Glu Ile Ser
 945 950 955 960
 Asp Ile Ala Arg Arg Gln Val Glu Ile Leu Asn Ala Gln Gln Gln Ser
 965 970 975
 Arg Asp Lys Glu Val
 980

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<210> SEQ ID NO 37
 <211> LENGTH: 973

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-continued

<212> TYPE: DNA
<213> ORGANISM: *Gallus domesticus*

<400> SEQUENCE: 37

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ggggggggagcg	gtctgggggg	tgcgtgcgtg	tgtgtgtgcg	tggggagcgc	cgcgtgcggc	180
tccgcgtgc	ccggggggctg	tgagcgctgc	gggcgcggcg	cggggctttg	tgcgctccgc	240
agtgtgcgcg	agggggagcgc	ggccgggggc	ggtgccccgc	ggtgcggggg	gggctgcgag	300
gggaacaaag	gctgcgtgcg	gggtgtgtgc	gtgggggggt	gagcaggggg	tgtgggcgcg	360
tccgtgggc	tgcaacccccc	cctgcacccc	cctcccccgag	ttgctgagca	cggcccccgc	420
tccgggtgcgg	ggctccgtac	ggggcgtggc	gcggggctcg	ccgtgccggg	cgggggggtgg	480
cggcaggtgg	gggtgcgggg	cggggcgggg	ccgcctcggg	cgggggaggg	ctcgggggag	540
gggcgeggcg	gccccccggag	cgcggcgggc	tgtcgaggcg	cgccgagccg	cagccattgc	600
cttttatgtt	aatcgtgcga	gagggcgcag	ggactttctt	tgtcccaaatt	ctgtcgaggag	660
ccgaaaatctg	ggagggcgccg	ccgcacccccc	tctagcgggc	gcggggcgaa	gcgggtgcggc	720
gcgggcagga	aggaaatggg	cggggagggc	cttcgtgcgt	cgccgcgcgc	ccgtccccctt	780
ctccctctcc	agcctcgggg	ctgtcccggg	ggggacggct	gccttcgggg	gggacggggc	840
agggcggggt	tcggcttctg	gcgtgtgacc	ggcggctcta	gagcctctgc	taaccatgtt	900
catgccttct	tcttttctt	acagctccctg	ggcaacgtgc	tggttattgt	gctgtctcat	960
cattttggca	aaq					973

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<210> SEQ ID NO 38
<211> LENGTH: 172
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide
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<400> SEQUENCE: 38

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gaactgaaaa accagaaagt taactggtaa gtttagtctt tttgtctttt atttcagggtc 60  
ccggatccgg tggtggtgca aatcaaagaa ctgctcctca gtggatgttg cctttacttc 120  
taggcctgtt cggaagtgtt acttctgtct taaaaggtgc ggaattgtac cc 172
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<210> SEQ ID NO 39
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: MBL intron
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<400> SEQUENCE: 39

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atccagcctc	cgcggccggg	aacggtgcat	tggaacgcgg	attccccgtg	ccaagagtga	120
cgttaagtacc	gcctatacgag	tctataggcc	caccccttg	gttcttatg	catgtatac	180
tgtttttggc	ttggggctta	tacaccccg	cttcctcatg	tttgctgccc	gtgaccagca	240
cgtcaacgat	tttgtggca	cgggcgacac	cgcagtgtag	tctgagcagt	actcggtct	300
gccgcgcgcg	ccaccagaca	taatagctga	cagactaaca	gactgttcct	ttccatgggt	360
cttttctgca	gtcacccgtcg	ccgc				384

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What is claimed is:

1. An isolated nucleic acid comprising a transgene encoding a CEP290 fragment having the amino acid sequence set forth in SEQ ID NO: 19 operably linked to a promoter, wherein the promoter is a retinotransferrin promoter, K12 promoter, a rhodopsin promoter, a rhodopsin kinase promoter, or an interphotoreceptor retinoid-binding protein proximal (IRBP) promoter, optionally wherein the rhodopsin kinase promoter is a GRK1 promoter.

2. The isolated nucleic acid of claim 1, wherein the CEP290 fragment is encoded by a nucleic acid having the sequence set forth in SEQ ID NO: 19.

3. The isolated nucleic acid of claim 1, wherein the transgene is flanked by adeno-associated virus (AAV) inverted terminal repeats (ITRs).

4. A recombinant adeno-associated virus (rAAV) comprising:

- (i) a capsid protein; and,
- (ii) the isolated nucleic acid of claim 1.

5. The rAAV of claim 4, wherein the capsid protein is AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAV9, or AAV10 capsid protein, optionally wherein the capsid protein comprises the sequence set forth in SEQ ID NO: 9.

6. A composition comprising the rAAV of claim 4, and a pharmaceutically acceptable excipient.

7. A recombinant adeno-associated virus (rAAV) vector comprising an expression cassette comprising a nucleic acid encoding the amino acid sequence set forth in SEQ ID NO: 19 operably linked to a promoter, wherein the expression cassette is flanked by adeno-associated virus 2 (AAV2) inverted terminal repeats (ITRs).

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8. The rAAV vector of claim 7, wherein the nucleic acid comprises the sequence set forth in SEQ ID NO: 29 or 34.

9. The rAAV vector of claim 7, wherein the expression cassette comprises an intron positioned between the promoter and the nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 19, optionally wherein the intron comprises a chicken beta-actin intron, a synthetic intron, or a MBL intron.

10. A recombinant adeno-associated virus (rAAV) comprising:

- (i) a nucleic acid encoding the amino acid sequence set forth in SEQ ID NO: 19 operably linked to a promoter, wherein the expression cassette is flanked by adeno-associated virus 2 (AAV2) inverted terminal repeats (ITRs); and
- (ii) one or more AAV capsid proteins.

11. The rAAV of claim 10, wherein the one or more AAV capsid proteins are AAV8 capsid proteins or AAV5 capsid proteins.

12. The rAAV of claim 10, wherein the promoter is a rhodopsin kinase (RK) promoter or a chicken beta-actin promoter.

13. The rAAV of claim 10 further comprising an intron positioned between the promoter and the nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 19.

14. The rAAV of claim 13, wherein the intron comprises a chicken beta-actin intron, a synthetic intron, or a MBL intron.

* * * * *