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(54) Title: TARGETED TRANS-SPLICING USING CRISPR/CAS13

(57) Abstract: This disclosure provides compositions and methods of using these compositions to mediate a targeted trans-splicing event on a pre-mRNA in a cell.



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TARGETED TRANS-SPLICING USING CRISPR/CAS13

RELATED APPLICATION

This application claims priority to U.S. Provisional Application Nos. 62/888,210, filed on August 16, 2019, and 62/985,633, filed on March 5, 2020, each of which is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with Government support under Grant No. HL141005 awarded by the National Institutes of Health (NIH). The Government has certain rights in the invention.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 14, 2020, is named 706829_083474-007PC_ST25.txt and is 475,491 bytes in size.

FIELD

The present disclosure relates to the field of CRISPR/Cas-mediated trans-splicing of nucleic acids for the treatment of disease.

BACKGROUND

Trans-splicing is a form of RNA processing where exons from two different primary pre-mRNA transcripts are joined end to end and ligated. This process is a promising strategy to treat various diseases using the spliceosome ribonucleoprotein complex. However, the efficiency and the specificity of trans-splicing of the current systems need to be improved upon to provide a more effective therapeutic strategy.

CRISPR/Cas systems have been used to edit genomic loci to treat diseases and disorders. This leads to a permanent edit to the DNA. The present invention provides a CRISPR/Cas system to target a trans-splicing element to a desired pre-mRNA sequence, and allows for the option of transient RNA repair while improving both the specificity and the efficiency of trans-splicing events.

SUMMARY

This disclosure provides methods and compositions for mediating a targeted trans-splicing event on a pre-mRNA in a cell. In one aspect, targeted trans-splicing system comprises: a nucleic acid-targeting CRISPR/Cas system; a nucleic acid guide; a specific RNA-binding domain; and a

repair template comprising a splice donor and/or acceptor and an RNA sequence that hybridizes under physiological conditions to the specific RNA-binding domain.

In various embodiments, the nucleic acid guide is a RNA guide. In various embodiments, the nucleic acid guide is a DNA guide. In various embodiments the trans-splicing system comprises one nucleic acid guide. In various embodiments, the trans-splicing system comprises more than one nucleic acid guide. In various embodiments, the nucleic acid guides recognize multiple targets. In various embodiments, the nucleic acid guide targets a splice acceptor (SA) site. In various embodiments, the nucleic acid guide targets a splice donor (SD) site. In various embodiments, the nucleic acid guide targets a region near a splice site. In various embodiments, the nucleic acid guide targets a region within 200 nucleotides of a splice site. In various embodiments, the nucleic acid guide targets a region less than or equal to 100 nucleotides from a splice site. In various embodiments, the more than one nucleic acid guides target one nucleic acid of interest. In various embodiments, the more than one nucleic acid guides target multiple nucleic acids of interest.

In various embodiments, the CRISPR/Cas system comprises a Cas13 polypeptide. In various embodiments, the Cas13 is a nuclease-inactive Cas13 polypeptide (dCas13). In various embodiments, the Cas13 is a nuclease-active Cas13 polypeptide. In various embodiments, the specific RNA-binding domain comprises a viral protein. In various embodiments, the viral protein is a MS2 binding protein. In various embodiments, **the viral protein is a λ N protein**. In various embodiments, the viral protein is a PP7 coat protein. In various embodiments, the viral protein is a QBeta coat protein.

In various embodiments, the viral protein is covalently bound to the CRISPR/Cas system. In various embodiments, the viral protein is not covalently bound to the CRISPR/Cas system. In various embodiments, the viral protein and CRISPR/Cas system is a fusion protein.

In one embodiment, the trans-splicing system comprises one repair template. In one embodiment, the trans-splicing system comprises more than one repair template. In various embodiments, the repair template is introduced as DNA. In various embodiments, the repair template is delivered as RNA.

In various embodiments, the repair template is expressed as RNA. In various embodiments, the repair template comprises a splice acceptor. In various embodiments, the repair template comprises a splice donor. In various embodiments, the repair template comprises one or more splice sites. In various embodiments, the repair template comprises an exon. In various embodiments, the repair template comprises more than one exon. In various embodiments, the repair template comprises an intron. the repair template comprises more than one intron. In various embodiments, the repair template comprises one or multiple sequences that hybridize to the target nucleic acid of interest. In various embodiments, at least one portion of the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein. In various embodiments, the repair template **comprises a boxB hairpin that specifically binds to the λ N protein**. In various embodiments, the repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein. In various

embodiments, the repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.

In various embodiments, the targeted trans-splicing system further comprises a cell. In various embodiments, at least one portion of the trans-splicing system is introduced into the cell.

5 In various embodiments, expression and/or activity of at least one portion of the trans-splicing system is transient. In various embodiments, the activity of at least one portion of the trans-splicing system is regulated by a small molecule. In various embodiments, the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, Cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903 / AP20187, and Auxin. In various embodiments, the at least one portion is a Cas13
10 protein. In various embodiments, the Cas13 protein further comprises a small molecule binding domain. In various embodiments, the Cas13 protein and the small molecule binding domain are linked by a glycine-serine linker. In various embodiments, the small molecule binding domain is an ABA-binding domain. In various embodiments, the ABA-binding domain comprises an ABI1 polypeptide.

15 In various embodiments, the targeted trans-splicing system further comprises a viral protein. In various embodiments, the viral protein further comprises a small molecule binding domain. In various embodiments, the viral protein and the small molecule binding domain are linked by a glycine-serine linker. In various embodiments, the small molecule binding domain is an ABA-binding domain. In various embodiments, the ABA-binding domain comprises a PYL1 polypeptide.
20 In various embodiments, the addition of ABA induces targeted trans-splicing of a target pre-mRNA.

In various embodiments, delivery of at least one portion of the trans-splicing system to the cell is viral. In various embodiments, the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus, or baculovirus. In various embodiments, delivery of at least one portion of the trans-splicing system to a cell is non-viral. In various embodiments, the non-viral
25 delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.

In various embodiments, the CRISPR/Cas system is targeted to a nucleic acid. In various embodiments, the nucleic acid is RNA. In various embodiments, the nucleic acid is DNA. In various embodiments, the CRISPR/Cas system is associated with RNA in the cell. In various embodiments, the RNA is a pre-mRNA. In various embodiments, the CRISPR/Cas system is associated with DNA
30 in the cell. In various embodiments, the CRISPR/Cas system is not associated with DNA in the cell. In various embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of the cell. In various embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell.

35 In various embodiments, the trans-splicing occurs in dividing cells. In various embodiments, the trans-splicing occurs in post-mitotic cells. In various embodiments, post-mitotic cells are neurons, myocytes, or adipocytes.

In various embodiments, expression of at least one portion of the trans-splicing system is inducible. In various embodiments, activity of at least one portion of the trans-splicing system is inducible.

5 In another aspect, provided herein is a method of mediating a targeted trans-splicing event on a pre-mRNA in a cell, the method comprises introducing at least one portion of a targeted trans-splicing CRISPR/Cas system into the cell. In one aspect, the CRISPR/Cas system comprises: a nucleic acid-targeting CRISPR/Cas system; a nucleic acid guide that specifically hybridizes to a nucleic acid locus of interest; a specific RNA-binding domain; and a repair template comprising a splice donor and/or a splice acceptor and an RNA sequence that hybridizes under physiological
10 conditions to the specific RNA-binding domain.

In one embodiment, the nucleic acid guide comprises RNA. In another embodiment, the nucleic acid guide comprises DNA.

In one embodiment, a single nucleic acid guide is introduced into the cell. In another embodiment, multiple nucleic acid guides are introduced into the cell.

15 In one embodiment, the multiple nucleic acid guides target one nucleic acid of interest. In another embodiment, the multiple nucleic acid guides target more than one nucleic acid of interest.

In various embodiments, the nucleic acid guide targets a splice acceptor (SA) site. In other embodiments, the nucleic acid guide targets a splice donor (SD) site.

In various embodiments, the nucleic acid guide targets a region near the splice site.

20 In various embodiments, the nucleic acid guide targets a region within 200 nucleotides of the splice site. In other embodiments, the nucleic acid guide targets a region less than or equal to 100 nucleotides of the splice site.

In various embodiments, a plurality of nucleic acid guides is delivered to a plurality of cells. In various embodiments, the CRISPR/Cas system comprises a Cas13 polypeptide.

25 In various embodiments, the Cas13 polypeptide is a Cas13b polypeptide. In various embodiments, the Cas13b polypeptide is a nuclease-inactive Cas13b (dCas13b). In various embodiments, the Cas13b polypeptide is a nuclease-active Cas13b.

In various embodiments, the specific RNA-binding domain comprises a viral protein. In various embodiments, the viral protein is a MS2 binding protein. In various embodiments, the viral
30 protein is a λ N protein.

In various embodiments, the viral protein is a PP7 coat protein. In various embodiments, the viral protein is a QBeta coat protein.

In various embodiments, the viral protein is covalently bound to the CRISPR/Cas system. In various embodiments, the viral protein is not covalently bound to the CRISPR/Cas system. In various
35 embodiments, the viral protein and CRISPR/Cas system is a fusion protein.

In various embodiments, the trans-splicing system comprises one splice acceptor repair template. In various embodiments, the trans-splicing system comprises more than one splice acceptor

repair template. In various embodiments, the trans-splicing system comprises one splice donor repair template.

In various embodiments, the trans-splicing system comprising more than one splice donor repair template.

5 In various embodiments, the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein. In various embodiments, the repair template comprises a boxB hairpin that **specifically binds to the λ N protein.**

10 In various embodiments, the repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein. In various embodiments, the repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.

In various embodiments, expression of at least one portion of the trans-splicing system is transient. In various embodiments, the activity of at least one portion of the trans-splicing system is transient. In various embodiments, the activity of at least one portion of the trans-splicing system is regulated by a small molecule. In various embodiments, the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, Cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903 / AP20187, and Auxin.

15 In various embodiments, at least one portion of the trans-splicing system comprises a Cas13 polypeptide. In various embodiments, the Cas13 polypeptide further comprises a small molecule binding domain.

20 In various embodiments, the Cas13 polypeptide and the small molecule binding domain are linked by a glycine-serine linker. In various embodiments, the small molecule binding domain is an ABA-binding domain.

In various embodiments, the ABA-binding domain comprises an ABI1 polypeptide. In various embodiments, the method further comprises a viral protein. In various embodiments, the viral protein further comprises a small molecule binding domain. In various embodiments, the viral protein and the small molecule binding domain are linked by a glycine-serine linker.

25 In various embodiments, the small molecule binding domain is an ABA-binding domain.

In various embodiments, the ABA-binding domain comprises a PYL1 polypeptide.

30 In various embodiments, the addition of ABA induces targeted trans-splicing of a target pre-mRNA.

In various embodiments, delivery of at least one portion of the trans-splicing system to a cell is viral.

In various embodiments, the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus or baculovirus.

35 In various embodiments, delivery of at least one portion of the trans-splicing system to a cell is non-viral.

In various embodiments, the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.

In various embodiments, the CRISPR/Cas system associates with RNA in the cell.

5 In various embodiments, the RNA is a pre-mRNA.

In various embodiments, the CRISPR/Cas system associates with DNA in the cell.

In various embodiments, the CRISPR/Cas system does not associate with DNA in the cell.

In various embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of the cell.

10 In various embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell.

In various embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at intron-exon junctions.

15 In various embodiments, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at exon-intron junctions.

In various embodiments, the splice repair template does not comprise a splice acceptor.

In various embodiments, the splice repair template does not comprise a splice donor.

In various embodiments, the splice repair template comprises both a splice acceptor and a splice donor.

20 In various embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at the 5' end of the pre-mRNA. In various embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at the 3' end of the pre-mRNA. In various embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at an internal site within a pre-mRNA. In various
25 untranslating region (UTR). In various embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA within the 5' untranslating region (UTR).

In various embodiments, the cell is a dividing cell. In various embodiments, the cell is a post-mitotic cell.

30 In various embodiments, the post-mitotic cell is selected from the group consisting of a neuron, myocyte, and adipocyte.

In various embodiments, expression of at least one portion of the trans-splicing system is inducible.

In various embodiments, activity of at least one portion of the trans-splicing system is inducible.

35 In various embodiments, the cell is in a subject suffering from a disease or disorder.

In various embodiments, the disease or disorder is a neurodegenerative, neurological, or neuromuscular disease or disorder.

In various embodiments, the neurodegenerative, neurological, or neuromuscular disease or disorder is selected from the group consisting of spinal muscular atrophy, Rett Syndrome, Angelman syndrome, Parkinson's disease, Alzheimer's disease, Huntington's disease, frontotemporal dementia, lysosomal storage diseases, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).

5 In yet another aspect, disclosed herein is a targeted trans-splicing system comprising: a nucleic acid binding protein domain; a specific RNA-binding domain; and a repair template comprising a splice donor and/or a splice acceptor and an RNA sequence that hybridizes under stringent conditions to the specific RNA-binding domain.

10 In various embodiments, the nucleic acid binding protein domain targets a splice acceptor (SA) site. In various embodiments, the nucleic acid binding protein domain targets a splice donor (SD) site. In various embodiments, the specific RNA-binding domain comprises a viral protein. In various embodiments, the viral protein is a MS2 binding protein. In various embodiments, the viral **protein is a λN protein**. In various embodiments, the viral protein is a PP7 coat protein. In various embodiments, the viral protein is a QBeta coat protein. In various embodiments, the viral protein is covalently bound to the nucleic acid binding protein domain. In various embodiments, the viral protein is not covalently bound to the nucleic acid binding protein domain. In various embodiments, the viral protein and nucleic acid binding protein domain is a fusion protein.

15 In various embodiments, the trans-splicing system comprises one splice acceptor repair template. In various embodiments, the trans-splicing system comprises more than one splice acceptor repair template. In various embodiments, the trans-splicing system comprises one splice donor repair template. In various embodiments, the trans-splicing system comprises more than one splice donor repair template. In various embodiments, the trans-splicing system comprises a repair template comprising a splice donor and/or a splice acceptor. In various embodiments, at least one portion of the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein. In various embodiments, the splice repair template comprises a boxB hairpin that specifically binds to **the λN protein**. In various embodiments, the splice repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein. In various embodiments, the splice repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.

20 In various embodiments, the targeted trans-splicing system further comprises a cell. In various embodiments, at least one portion of the trans-splicing system is introduced into the cell.

25 In various embodiments, expression and/or activity of at least one portion of the trans-splicing system is transient. In various embodiments, the activity of at least one portion of the trans-splicing system is regulated by a small molecule. In various embodiments, the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, Cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903/AP20187, and Auxin. In various embodiments, at least one portion is the nucleic acid binding protein domain. In various embodiments, the nucleic acid binding protein domain further comprises a small molecule binding domain. In various embodiments, the nucleic acid

binding protein domain and the small molecule binding domain are linked by a glycine-serine linker. In various embodiments, the small molecule binding domain is an ABA-binding domain. In various embodiments, the ABA-binding domain comprises an ABI1 polypeptide. In various embodiments, the trans-splicing system further comprises a viral protein. In various embodiments, the viral protein further comprises a small molecule binding domain. In various embodiments, the viral protein and the small molecule binding domain are linked by a glycine-serine linker. In various embodiments, the small molecule binding domain is an ABA-binding domain. In various embodiments, the ABA-binding domain comprises a PYL1 polypeptide. In various embodiments, the addition of ABA induces targeted trans-splicing of a target pre-mRNA.

In various embodiments, delivery of at least one portion of the trans-splicing system to the cell is viral. In various embodiments, the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus, or baculovirus. In various embodiments, delivery of at least one portion of the trans-splicing system to a cell is non-viral. In various embodiments, the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.

In various embodiments, the nucleic acid binding protein domain is targeted to DNA. In various embodiments, the nucleic acid binding protein domain is targeted to RNA. In various embodiments, the nucleic acid binding protein domain is associated with RNA in the cell. In various embodiments, the RNA is a pre-mRNA. In various embodiments, the nucleic acid binding protein domain is associated with DNA in the cell. In various embodiments, the nucleic acid binding protein domain is not associated with DNA in the cell.

In various embodiments, the system mediates trans-splicing of pre-mRNA in the nucleus of the cell. In various embodiments, the system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell. In various embodiments, the system mediates trans-splicing of a pre-mRNA at intron-exon junctions. In various embodiments, the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA at exon-intron junctions. In various embodiments, the splice repair template does not comprise a splice donor. In various embodiments, the splice repair template does not comprise a splice acceptor. In various embodiments, the splice repair template comprises both a splice acceptor and a splice donor.

In various embodiments, the system comprises multiple splice templates. In various embodiments, the multiple splice templates comprise splice repair templates that comprise a splice acceptor and splice repair templates that comprise a splice donor. In various embodiments, at least some of the multiple splice repair templates comprise a splice acceptor and a splice donor.

In various embodiments, the system mediates trans-splicing of a pre-mRNA at the 5' end of the pre-mRNA. In various embodiments, the system mediates trans-splicing of a pre-mRNA at the 3' end of the pre-mRNA. In various embodiments, the system mediates trans-splicing of a pre-mRNA at

an internal site within a pre-mRNA. In various embodiments, the system replaces the 5' or the 3' end of the target mRNA.

In various embodiments, the target mRNA is a pre-mRNA. In various embodiments, the system comprises replacing one or more exons of the target mRNA, excluding the first and last exon of the target mRNA. In various embodiments, the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA within the 3' untranslated region (UTR). In various embodiments, the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA within the 5' untranslated region (UTR).

In various embodiments, the trans-splicing occurs in dividing cells. In various embodiments, the trans-splicing occurs in post-mitotic cells. In various embodiments, the post-mitotic cells are neurons, myocytes, or adipocytes.

In various embodiments, expression of at least one portion of the trans-splicing system is inducible. In various embodiments, activity of at least one portion of the trans-splicing system is inducible. In various embodiments, the nucleic acid binding protein domain is a domain from a zinc finger nuclease (ZFNs) or a Pumby module, or is an RNA recognition motif.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1A-1E illustrates the components of the CRISPR/Cas system, cis- and trans-splicing that can occur within a pre-mRNA, and the CRISPR-mediated trans-splicing.

FIG. 2A illustrates the DNA constructs encoding the endoribonuclease-inactive Cas13 (dCas13b)-MS2 fusion protein, the gRNA construct, the splice donor (SD) and splice acceptor (SA) reporters, and the ms2 intron design. **FIG. 2B** illustrates the trans-splicing reporter assay.

FIG. 3A illustrates the trans-splicing activity of the CRISPR/Cas system compared to negative controls in HEK193FT cells. Columns 1-5 represent activity in the negative controls. Column 11 is the activity of the CRISPR/Cas system. **FIG. 3B** illustrates the trans-splicing specificity of the CRISPR/Cas system. RNAseq libraries were created using primers that bind to the SA reporter mRNA, and on-target reactions of reads were calculated and plotted.

FIG. 4A is RNAseq mapping of RNAseq libraries to demonstrate trans-splicing. **FIG. 4B** illustrates validation that there was cis-splicing of the SD reporter.

FIG. 5 is a schematic of gRNA target sites. Several gRNAs were designed to target different regions of the SD reporter.

FIG. 6A illustrates fold-increase in targeted trans-splicing with dCas13b-MS2 as measured by using a truncated GFP trans-splicing reporter assay. **FIG. 6B** illustrates the targeted trans-splicing without dCas13b-MS2.

FIG. 7 is a schematic that illustrates the components of the CRISPR/Cas system in trans-splicing in the context of correcting a pathogenic exon.

FIG. 8 illustrates induction of the trans-splicing complex with a small molecule. **FIG. 8A** illustrates a dCas13b polypeptide fused to abscisic acid (ABA)-binding protein ABI1, and MS2 fused to PYL1. **FIG. 8B** is a graph demonstrating expression of GFP after induction of trans-splicing in the presence of a range of ABA concentrations, shown with a no guide control as a negative control.

FIG. 8C demonstrates that ABA could control induced targeted trans-splicing by measuring fold-increase in expression of GFP with increasing concentrations of ABA (mM).

FIG. 9 is a measurement of trans-splicing at splice junctions. **FIG. 9A** illustrates RNAseq reads spanning possible junctions. **FIG. 9B** is a plot of spliced reads that were trans-spliced for all transfection conditions. **FIG. 9C** is a plot of spliced reads that were cis-spliced for all transfection conditions.

FIG. 10 is an illustration of strategies for targeted trans-splicing. **FIG. 10A** illustrates a strategy for 5' targeting of trans-splicing. **FIG. 10B** illustrates an internal targeted trans-splicing strategy. **FIG. 10C** illustrates a strategy for 3' targeting of trans-splicing.

FIG. 11 illustrates a strategy for internal exon repair. **FIG. 11A** illustrates dPspCas13b-MS2, gRNA, target and internal repair template constructs to test if CRISPR-mediated internal exon repair is possible. **FIG. 11B** illustrates monitoring of expression of the target transcript via expression of blue fluorescent protein (BFP), and monitoring internal exon repair via expression of green fluorescent protein (GFP). **FIG. 11C** measures GFP expression following internal exon repair, demonstrating that GFP expression is only possible in the presence of the CRISPR system along with gRNAs targeting splice sites.

FIG. 12 is fluorescence measurements to illustrate that trans-splicing can be mediated using other Cas13 orthologs, such as Cas13d.

FIG. 13 demonstrates CRISPR-mediated trans-splicing accomplished with a construct delivered with a multi-vector AAV-based approach.

DETAILED DESCRIPTION

This disclosure provides compositions and methods of using these compositions to mediate a targeted trans-splicing event on a pre-mRNA in a cell. In various embodiments, the targeted trans-splicing event is mediated by a CRISPR/Cas system. In various embodiments, the CRISPR/Cas system that mediates a targeted trans-splicing event is used to treat a neurodegenerative disease or disorder. These compositions and methods include a trans-splicing event mediated by a CRISPR/Cas system comprising a nuclease-inactive Cas13.

As used within the Claims, the Summary, and the Detailed Description herein, the term “a” or “an” entity refers to one or more of that entity; for example, “a cell” is understood to represent one or more cells.

Furthermore, “and/or” where used herein is to be taken as specific disclosure of each of the two specified features of components with or without the other. Thus, the term “and/or” as used in a

phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone).

It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” are also provided.

5 The term “near a splice site” means within 500 bp of a splice site.

The term “treatment” refers to the application of one or more specific procedures used for the amelioration of a disease. In certain embodiments, the specific procedure is the administration of one or more pharmaceutical agents. “Treatment” of an individual (*e.g.* a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell.

10 Treatment includes, but is not limited to, administration of a pharmaceutical composition, and may be performed either prophylactically or subsequent to the initiation of a pathologic event or contact with an etiologic agent. Treatment includes any desirable effect on the symptoms or pathology of a disease or condition, and may include, for example, minimal changes or improvements in one or more measurable markers of the disease or condition, and may include, for example, minimal changes or
15 improvements in one or more measurable markers of the disease or condition being treated.

The terms “patient,” “subject,” “individual,” and the like are used interchangeably herein, and refer to any animal, or cells thereof whether *in vitro* or *in situ*, amenable to the methods described herein. In certain non-limiting embodiments, the patient, subject, or individual is a human.

In aspects of the invention the terms “guide nucleic acid,” “RNA guide,” “DNA guide,” and
20 “single guide nucleic acid,” are used interchangeably and refer to the polynucleotide sequence comprising the guide sequence, and the tracr sequence. In certain embodiments, the guide nucleic acid comprises only a crispr RNA (crRNA). The term “guide sequence” refers to a 10-80 bp sequence within the RNA or DNA guide that specifies the target site. In aspects of the invention, the terms “guide sequence” and “spacer” are used interchangeably. In aspects of the invention, the terms “direct
25 repeat” and “scaffold” are used interchangeably.

As used herein, “stringent conditions” for hybridization refer to conditions under which a nucleic acid having complementarity to a target sequence predominantly hybridizes with the target sequence, and substantially does not hybridize to non-target sequences. Stringent conditions are generally sequence-dependent, and vary depending on a number of factors. In general, the longer the
30 sequence, the higher the temperature at which the sequence specifically hybridizes to its target sequence. In some embodiments, stringent conditions include hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45° C., followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65° C. Other examples of stringent conditions are known to those skilled in the art and can be found in Current Protocols in Molecular Biology, Ausubel *et al.*, eds., John Wiley & Sons, Inc.
35 (1995), sections 2, 4, and 6, the teachings of which are hereby incorporated by reference herein. Additional stringent conditions can be found in Molecular Cloning: A Laboratory Manual, Sambrook

et al., Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (1989), chapters 7, 9, and 11, the teachings of which are hereby incorporated by reference herein.

As used herein, the term “physiological condition” typically refers to biologic parameters that are valid for an animal, specifically a mammal, more specifically a human. The term may relate to biochemical and biophysical parameters commonly found in mammals, especially in the human body (especially body fluids). The “physiological condition” may relate to parameters found in a sick mammal or human patient, as well as that corresponding parameters found in a healthy body. For example, a sick mammal or human patient may have a high but “physiological” temperature condition when the mammal or the human is suffering from a fever. Regarding “physiological conditions” the most important parameters are temperature (37 °C for human body), pH (7.35-7.45 for human blood), osmotic pressure (280-300 mmol / Kg H₂O) and, if necessary, protein content (66-85 g / l serum). However, those skilled in the art will appreciate that these parameters may vary. For example, such temperature, pH, osmotic pressure, and protein content may be different in a given body or tissue, such as blood or cerebrospinal fluid (Klinke (2005) Physiologie, 5th ed., Georg Thieme Verlag, Stuttgart). “Physiological condition” can also refer to conditions in a buffer system, solvent, and/or excipient that mimic conditions in an animal.

“Hybridization” or “hybridizes” refers to a reaction in which one or more polynucleotides react to form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues. The hydrogen bonding may occur by Watson-Crick base pairing, Hoogsteen binding, or in any other sequence-specific manner. The complex may comprise two strands forming a duplex structure, three or more strands forming a multi-stranded complex, a single self-hybridizing strand, or any combination of these.

As used herein, “expression” refers to the process by which a polynucleotide is transcribed from a DNA template (such as into a mRNA or other RNA transcript) and/or the process by which a transcribed mRNA is subsequently translated into peptides, polypeptides, or proteins. Transcripts and encoded polypeptides may be collectively referred to as “gene product.” If the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in a eukaryotic cell.

The terms “polypeptide,” “peptide,” “protein,” and “enzyme” are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. As used herein the term “amino acid” includes natural and/or unnatural or synthetic amino acids, including glycine and both the D or L optical isomers, and amino acid analogs and peptidomimetics.

The term “nucleic acid” or “nucleic acid sequence” refers to a deoxyribonucleic or ribonucleic oligonucleotide in either single- or double-stranded form. The term encompasses nucleic acids, *i.e.*,

oligonucleotides, containing known analogues of natural nucleotides. The term also encompasses nucleic-acid-like structures with synthetic backbones, see, *e.g.*, Eckstein, *Biomed Biochim Acta*. 1991;50(10-11):S114-7; Baserga *et al.* *Genes Dev.* 1992 Jun;6(6):1120-30; Milligan *et al.*, *Nucleic Acids Res.* 1993 Jan 25;21(2):327-33; WO 97/03211; WO 96/39154; Mata, *Toxicol Appl Pharmacol.* 1997 May;144(1):189-97; Strauss-Soukup, *Biochemistry.* 1997 Aug 19;36(33):10026-32; and Samstag, *Antisense Nucleic Acid Drug Dev.* 1996 Fall;6(3):153-6.

“Inducible” as used herein refers to inducing expression or activity of a protein or a system, *e.g.*, the trans-splicing system of the instant application. Known inducible gene expression systems have been designed to allow for chemically induced activation of an inserted nucleic acid sequence, resulting in gene overexpression or repression. Inducing activity of a protein or system can include release of a molecule to allow for activity or the addition of an effector molecule to induce activity of a protein or system.

The term “nuclease-inactive” is used to describe a Cas enzyme which no longer has nuclease activity. In some embodiments, a Cas enzyme that no longer has nuclease activity can have a small amount of residual activity. In some embodiments, this small amount of residual activity is less than 5, 1, 0.1, 0.05, 0.01 or 0.005% of wild type nuclease activity of the Cas enzyme. A nuclease-inactive Cas protein may interchangeably be referred to as a “dCas” protein, *e.g.*, dCas13b. In some embodiments, the dCas protein can be a dCas13b protein. In some embodiments, a polynucleotide sequence set forth in SEQ ID NOs: 1, 62, 71, 74, 77, 80, 83, 86, or 89 encodes a dCas13b protein. In some embodiments, dCas13b corresponds to, or comprises in part or in whole, the amino acid sequence set forth as SEQ ID NOs: 2, 63, 72, 75, 78, 81, 84, 87, or 90. In some embodiments, the dCas protein can be a dCas13a protein. In some embodiments, a dCas13a protein is encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, or 59. In some embodiments, dCas13a corresponds to, or comprises in part or in whole, any one of the amino acid sequence set forth as SEQ ID NOs: 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, or 60. In some embodiments, the dCas protein can be a dCas13d protein. In some embodiments, the dCas13d protein is encoded by the polynucleotide sequence set forth in SEQ ID NO: 65. In some embodiments, the dCas13d protein corresponds to, or comprises in part or in whole, the amino acid sequence set forth in SEQ ID NO: 66. Nuclease-inactive Cas proteins may be variants having mutations which result in nuclease activity inactivated.

“Targeted” is used to describe a molecule, protein, or complex that comprise a targeting moiety which specifically binds to one or more targets associated with a specific pre-mRNA of interest.

As used herein, the term “RNA-binding” is used to describe a molecule, protein, nucleic acid, or complex that specifically binds to RNA.

“Pre-mRNA” refers to a precursor mRNA and is an RNA which contains both exons and intron(s). Pre-mRNA is a type of primary transcript that becomes a messenger RNA after processing.

It is synthesized from a DNA template in the cell nucleus by transcription. In some embodiments, RNA is from a mammalian cell. In other embodiments, the RNA is from the mitochondria of a mammalian cell.

The phrase “associates with DNA” refers to nucleic acids, systems, proteins, and molecules that may bind or be in the same vicinity as DNA.

The term “post-mitotic” refers to a non-replicating cell, such as a cell of the nervous system, bone marrow cells, muscle cells, liver cells, and the like. Cells of the nervous system include neurons, glial cells, etc. that is no longer capable of undergoing mitosis.

The term “non-dividing cells” refers to a cell that does not frequently undergo mitosis. Many non-dividing cells may be blocked at any point in the cell cycle (*e.g.*, G0/G1, G1/S, G2/M), as long as most of the cells are not actively dividing. In some embodiments, non-dividing cells are from tissue types that do not frequently divide. Examples of non-dividing cells in the body include, but are not limited to, neuronal, muscle (myocytes), liver, skin, heart, lung, adipose, and bone marrow cells, and their derivatives. “Dividing cells” would be a cell that frequently actively undergoes mitosis. In some embodiments, dividing cells are from tissue types that do not frequently divide. Examples of dividing cells in the body include, but are not limited to, epithelial cells and hematopoietic cells.

A “disease” is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal’s health continues to deteriorate. In contrast, a “disorder” in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal’s state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal’s state of health. Diseases and disorders include spinal muscular atrophy, Rett Syndrome, Angelman syndrome, Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, frontotemporal dementia, lysosomal storage diseases, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).

A “vector” is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term “vector” includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, herpes simplex virus, anellovirus, baculovirus, retroviral vectors, and the like.

The term “specifically binds,” or the like, means that a given molecule forms a complex with another molecule that is relatively stable under physiologic conditions. Methods for determining whether a given molecule specifically binds to another molecule are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an

RNA hairpin that "specifically binds" a viral protein, as used herein, includes RNA hairpins that bind viral proteins or a portion thereof with a KD of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or about 0.5 nM, as measured in a surface plasmon resonance assay.

"Variant" as used herein means a polypeptide or nucleotide sequence that differs from a given polypeptide or nucleotide sequence in amino acid or nucleic acid sequence by the addition (*e.g.*, insertion), deletion, or conservative substitution of amino acids or nucleotides, but that retains the biological activity of the given polypeptide (*e.g.*, a variant nucleic acid could still encode the same or a similar amino acid sequence). A conservative substitution of an amino acid, *i.e.*, replacing an amino acid with a different amino acid of similar properties (*e.g.*, hydrophilicity and degree and distribution of charged regions) is recognized in the art as typically involving a minor change. These minor changes can be identified, in part, by considering the hydropathic index of amino acids, as understood in the art (see, *e.g.*, Kyte *et al.*, J. Mol. Biol., 157: 105-132 (1982)). The hydropathic index of an amino acid is based on a consideration of its hydrophobicity and charge. It is known in the art that amino acids of similar hydropathic indexes can be substituted and still retain protein function. In one aspect, amino acids having hydropathic indexes of ± 2 are substituted. The hydrophilicity of amino acids also can be used to reveal substitutions that would result in proteins retaining biological function. A consideration of the hydrophilicity of amino acids in the context of a peptide permits calculation of the greatest local average hydrophilicity of that peptide, a useful measure that has been reported to correlate well with antigenicity and immunogenicity (see, *e.g.*, U.S. Pat. No. 4,554,101). Substitution of amino acids having similar hydrophilicity values can result in peptides retaining biological activity, for example immunogenicity, as is understood in the art. In one aspect, substitutions are performed with amino acids having hydrophilicity values within ± 2 of each other. Both the hydrophobicity index and the hydrophilicity value of amino acids are influenced by the particular side chain of that amino acid. Consistent with that observation, amino acid substitutions that are compatible with biological function are understood to depend on the relative similarity of the amino acids, and particularly the side chains of those amino acids, as revealed by the hydrophobicity, hydrophilicity, charge, size, and other properties. "Variant" also can be used to describe a polypeptide or fragment thereof that has been differentially processed, such as by proteolysis, phosphorylation, or other post-translational modification, yet retains its biological activity or antigen reactivity. Use of "variant" herein is intended to encompass fragments of a variant unless otherwise contradicted by context.

Alternatively or additionally, a "variant" is to be understood as a polynucleotide or protein which differs in comparison to the polynucleotide or protein from which it is derived by one or more

changes in its length or sequence. The polypeptide or polynucleotide from which a protein or nucleic acid variant is derived is also known as the parent polypeptide or polynucleotide. The term "variant" comprises "fragments" or "derivatives" of the parent molecule. Typically, "fragments" are smaller in length or size than the parent molecule, whilst "derivatives" exhibit one or more differences in their sequence in comparison to the parent molecule. Also encompassed modified molecules such as but not limited to post-translationally modified proteins (*e.g.* glycosylated, biotinylated, phosphorylated, ubiquitinated, palmitoylated, or proteolytically cleaved proteins) and modified nucleic acids such as methylated DNA. Also mixtures of different molecules such as but not limited to RNA-DNA hybrids, are encompassed by the term "variant". Typically, a variant is constructed artificially, preferably by gene-technological means whilst the parent polypeptide or polynucleotide is a wild-type protein or polynucleotide. However, also naturally occurring variants are to be understood to be encompassed by the term "variant" as used herein. Further, the variants usable in the present disclosure may also be derived from homologs, orthologs, or paralogs of the parent molecule or from artificially constructed variant, provided that the variant exhibits at least one biological activity of the parent molecule, *i.e.* is functionally active.

Alternatively, or additionally, a "variant" as used herein, can be characterized by a certain degree of sequence identity to the parent polypeptide or parent polynucleotide from which it is derived. More precisely, a protein variant in the context of the present disclosure exhibits at least 80% sequence identity to its parent polypeptide. A polynucleotide variant in the context of the present disclosure exhibits at least 70% sequence identity to its parent polynucleotide. The term "at least 70% sequence identity" is used throughout the specification with regard to polypeptide and polynucleotide sequence comparisons. This expression preferably refers to a sequence identity of at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the respective reference polypeptide or to the respective reference polynucleotide.

The similarity of nucleotide and amino acid sequences, *i.e.* the percentage of sequence identity, can be determined via sequence alignments. Such alignments can be carried out with several art-known algorithms, preferably with the mathematical algorithm of Karlin and Altschul (Karlin & Altschul (1993) Proc. Natl. Acad. Sci. USA 90: 5873-5877), with hmalign (HMMER package, <http://hmmer.wustl.edu/>) or with the CLUSTAL algorithm (Thompson, J. D., Higgins, D. G. & Gibson, T. J. (1994) Nucleic Acids Res. 22, 4673-80) available *e.g.* on <http://www.ebi.ac.uk/Tools/clustalw/> or on <http://www.ebi.ac.uk/Tools/clustalw2/index.html> or on http://npsa-pbil.ibcp.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_clustalw.html. Preferred parameters used are the default parameters as they are set on <http://www.ebi.ac.uk/Tools/clustalw/> or <http://www.ebi.ac.uk/Tools/clustalw2/index.html>. The grade of sequence identity (sequence

matching) may be calculated using *e.g.* BLAST, BLAT or BlastZ (or BlastX). A similar algorithm is incorporated into the BLASTN and BLASTP programs of Altschul *et al.* (1990) J. Mol. Biol. 215: 403-410. To obtain gapped alignments for comparative purposes, Gapped BLAST is utilized as described in Altschul *et al.* (1997) Nucleic Acids Res. 25: 3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs are used. Sequence matching analysis may be supplemented by established homology mapping techniques like Shuffle-LAGAN (Brudno M., Bioinformatics 2003b, 19 Suppl 1:I54-I62) or Markov random fields. When percentages of sequence identity are referred to in the present application, these percentages are calculated in relation to the full length of the longer sequence, if not specifically indicated otherwise.

Trans-Splicing

A number of gene therapy techniques have been devised to address specific pathologies. These different approaches range from gene supplementation using viral vectors to genome editing using CRISPR/Cas9 technology. However, there are times when these approaches are not applicable or effective to achieve significant therapeutic effect. Currently, there are efforts to address this problem by repairing mutant transcripts to make clean transcripts without altering gene expression levels by exploiting the spliceosome to catalyze therapeutic trans-splicing events. (See, *e.g.*, FIG. 7).

Splicing is a reaction found in the nucleus of eukaryotic cells catalyzed by the spliceosome, a large ribonucleoproteic complex. Splicing results in the elimination of introns in the pre-mRNA. This reaction is considered cis-splicing as it involves a donor site, a branch point, and an acceptor site located on the same RNA molecule.

The spliceosome can also catalyze trans-splicing events. Unlike cis-splicing, trans-splicing occurs between two different RNA molecules. The molecular process is the same, except that the final mRNA is composed of the first exon(s) of the first pre-mRNA and the exon(s) of another, thus creating a chimeric molecule. With the discovery of naturally occurring trans-splicing, it was demonstrated to be useful for bioengineering purposes. In 1999, Puttaraju *et al.* (Nature Biotech., 17:246-52) demonstrated the ability of diverting trans-splicing to induce repair of an endogenous mRNA using exon exchange mediated by an artificial RNA capable of inducing trans-splicing in cell culture. Subsequent studies showed the feasibility of using this *in vivo*, leading to the functional restoration of mutant cystic fibrosis transmembrane conductance regulator (CFTR) in a human bronchial xenograft model system. This led to the study of and use of the spliceosome-mediated RNA trans-splicing, or SMaRT system, as a gene therapy strategy. While this technology has been used to mediate repair of various mRNA sequences associated with disease, there are drawbacks and limitations to the SMaRT technology.

There are some important drawbacks to the current SMaRT technology that one must take into account. One drawback of the SMaRT technology is the specificity of the molecule. Theoretically, off-target trans-splicing with random mRNAs should be processed by nonsense

mediated decay or nonstop decay, it is essential to validate the specificity of the pre-mRNA trans-splicing molecule for the target sequence and limit nonspecific events. It has been found that increasing the length of the binding domain sequence up to 153 bases dramatically decreases the probability of finding the entire and exact corresponding sequence in a human genome and increases efficiency. Another drawback is the efficiency of the system. With certain diseases, even a low level of expression of the mutated protein will lead to a diseased phenotype.

CRISPR/Cas

The present disclosure includes compositions and methods that comprise a targeted trans-splicing system comprising a nuclease-inactive CRISPR/Cas system, a nucleic acid guide, a specific RNA-binding domain, and a repair template comprising an RNA sequences that hybridizes under stringent conditions to the specific RNA-binding domain. Clustered regularly interspaced short palindromic repeats, known more widely as CRISPR, and a family of enzymes known as Cas (CRISPR-associated) proteins is a prokaryotic immune system that confers resistance to foreign genetic elements such as those present within plasmids and phages that provides a form of acquired immunity. Recently, CRISPR/Cas systems have been developed as tools used in basic molecular biology research, the development of biotechnology products, and treatment of disease. These systems have been widely adopted for mediating targeted DNA cleavage which in turn drives targeted gene disruption through non-homologous end joining (NHEJ) or precise gene editing through template-dependent homology-directed repair (HDR).

In certain embodiments, the CRISPR/Cas system described herein comprises a Cas13 enzyme encoded by a polynucleotide sequence of any one of SEQ ID NOs: 1, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 71, 74, 77, 80, 83, 86, or 89 or variants thereof. In certain embodiments, the CRISPR/Cas system comprises a Cas13 enzyme comprising an amino acid sequence of any one of SEQ ID NOs: 2, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 72, 75, 78, 81, 84, 87, or 90 or variants thereof. Cas13 enzymes are classified as Type VI CRISPR-Cas systems and have two Higher Eukaryotes and Prokaryotes Nucleotide-binding (HEPN) endoRNase domains that mediate precise RNA cleavage with a preference for targets with protospacer flanking site motif observed biochemically and in bacteria. Three Cas13 protein families have been identified to date. Cas13a, previously known as C2c2, can be adapted as tools for nucleic acid detection. Cas13b has been used for both RNA editing and nucleic acid detection, and is unique among the type VI CRISPR effectors in its linear domain architecture and CRISPR RNA (crRNA) structures. Cas13 enzymes are programmable in nature, and makes them an attractive starting point to develop tools for RNA binding and perturbation applications (Cox *et al.* (2017) Science. 358:1019-1027, incorporated by reference herein in its entirety).

The term “nucleic acid binding protein domain” refers to a domain of a protein that is capable of targeting a specific nucleic acid sequence. In some embodiments, the nucleic acid sequence is

DNA. In other embodiments, the nucleic acid sequence is RNA. In some embodiments, the nucleic acid binding protein domain specifically binds to a splice acceptor or a splice donor site. Some examples of nucleic acid binding protein domains include, but are not limited to, zinc finger nucleases (ZFNs), and Pumby modules (Adamala *et al.* (2016) *Proc Natl Acad Sci.* 113(19):E2579-E2588, incorporated by reference herein in its entirety), or humanized CRISPR, e.g., CRISPR-Cas-Inspired RNA Targeting System (CIRTS) (Rauch *et al.* (2019) *Cell.* 178(1):P122-134, incorporated by reference herein in its entirety), or RNA recognition motif (Maris *et al.* (2005) *The FEBS journal* 272: 2118-2131).

The RNA-targeting systems, the vector systems, the vectors and the compositions described herein may be used in various RNA-targeting applications, altering or modifying synthesis of a gene product, such as a protein, RNA cleavage, RNA editing, RNA splicing; trafficking of target RNA, tracing of target RNA, isolation of target RNA, visualization of target RNA, etc.

The term “splice donor” refers to the 5' end of the intron.

The term “splice acceptor” refers to the 3' end of the intron.

The term “repair template” refers to a nucleic acid molecule with comprising a desired sequence to be spliced to a nucleic acid locus of interest. In some embodiments, the desired sequence to be spliced is an exon. In some embodiments, the repair template further comprises one or more introns.

In certain embodiments, the nucleic acid guide is a RNA guide. In certain embodiments, the nucleic acid guide is a DNA guide. In some embodiments, the guide nucleic acid, such as a guide RNA or gRNA, is a specific sequence that recognizes the target pre-mRNA of interest and directs the Cas protein to said pre-mRNA. In some embodiments, the guide nucleic acid targets the DNA locus where transcription is occurring. Generally, the guide nucleic acid is made of two components – a crRNA, which is a 17-20 nucleotide sequence complementary to the target sequences, and a tracr RNA, which serves as a binding scaffold for the Cas nuclease. More recently, the crRNA and tracr RNA components have been fused into one molecule to create a single guide RNA (sgRNA). In certain embodiments, the trans-splicing system comprises one nucleic acid guides. For currently characterized CRISPR/Cas13 systems, a crRNA (crRNA) is comprised of a spacer and a direct repeat. For Cas13b, the spacer is 5' and the direct repeat is the 3' of the crRNA. For Cas13b, crRNA and guide RNA can be used interchangeably. For Cas13a and Cas13d, the spacer is 3' and the direct repeat is the 5' of the crRNA (Zhang F (2019). *Development of CRISPR-Cas systems for genome editing and beyond. Quarterly Reviews of Biophysics* 52, e6, 1–31. <https://doi.org/10.1017/S0033583519000052>, incorporated by reference herein in its entirety). In certain embodiments, the trans-splicing system comprises more than one nucleic acid guide. In certain embodiments, more than one nucleic acid guides are in an array operably linked to one promoter, which are then cleaved and processed by Cas13. In some embodiments, an array has direct repeats between multiple spacers wherein each spacer targets a different nucleic acid. In certain embodiments, more than one nucleic

acid guides are expressed by separate promoters, such as U6 promoters. In certain embodiments, the guide RNAs have a direct repeat (*e.g.*, SEQ ID NOs: 10, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 73, 76, 79, 82, 85, 88, and 91) at the 5' end, and a spacer at the 3' end. In other embodiments, the guide RNAs have a direct repeat (*e.g.*, SEQ ID NOs: 10, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 73, 76, 79, 82, 85, 88, and 91) at the 3' end, and a spacer at the 5' end. In other embodiments, spacers are flanked by direct repeats (*e.g.*, SEQ ID NOs: 10, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 73, 76, 79, 82, 85, 88, and 91). In certain embodiments, the direct repeats have at least 70% (*e.g.*, at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity with the direct repeat nucleic acid sequences of SEQ ID NOs: 10, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 73, 76, 79, 82, 85, 88, or 91. In certain embodiments, the nucleic acid guides recognize multiple targets. In certain embodiments, the instant disclosure provides nucleic acid guide sequences having at least 70% (*e.g.*, at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity with the nucleic acid sequence of SEQ ID NO: 11 or 12.

The invention uses nucleic acids to bind target RNA sequences. This is advantageous as nucleic acids are much easier and cheaper to produce than proteins, and the specificity can be varied according to the length of the stretch where homology is sought. Complex 3-D positioning of multiple fingers, for example is not required. The terms “polynucleotide”, “nucleotide”, “nucleotide sequence”, “nucleic acid” and “oligonucleotide” are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, short interfering RNA (siRNA), short-hairpin RNA (shRNA), micro-RNA (miRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. The term also encompasses nucleic-acid-like structures with synthetic backbones, see, *e.g.*, Eckstein, 1991; Baserga et al., 1992; Milligan, 1993; WO 97/03211; WO 96/39154; Mata, 1997; Strauss-Soukup, 1997; and Samstag, 1996. A polynucleotide may comprise one or more modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component.

In certain embodiments, the specific RNA binding domain of the CRISPR/Cas system comprises a viral protein fused to the Cas protein. The term “viral protein” can be used to describe a protein of viral origin that is bound to the Cas protein that binds to a hairpin of the splice acceptor template. Coat proteins of single-stranded RNA bacteriophages are translational repressors of viral replicase. They accomplish this by specifically binding an RNA hairpin that encompasses the replicase start codon. Some examples would be the coat proteins of RNA phages MS2, λ N, QBeta, and PP7 (*e.g.* SEQ ID NOs: 5-9). In certain embodiments, the specific RNA binding domain comprises an amino acid sequence of any one of SEQ ID NOs: 6, 7, 8, or 9, or variants thereof. The term “binding”, or the like, means that a viral protein forms a complex with a corresponding hairpin that is relatively stable under physiologic conditions. In certain embodiments, the instant disclosure provides hairpin sequences having at least 70% (*e.g.*, at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity with any one of the nucleic acid sequences of SEQ ID NOs: 13-16.

In certain embodiments, the viral protein is covalently bound to the CRISPR/Cas system. In certain embodiments, the viral protein is not covalently bound to the CRISPR/Cas system. In certain embodiments, the viral protein and CRISPR/Cas system is a fusion protein. As used herein, the term “covalently bound” refers to a chemical bond that involves the sharing of electrons between atoms. The term “fusion protein” refers to proteins created through the joining of two or more genes that originally coded for separate proteins.

In some embodiments, the specific RNA binding domain of the CRISPR/Cas system comprises an RNA binding protein that is not of viral origin.

In certain embodiments, the trans-splicing system comprises one repair template. In certain embodiments, the trans-splicing system comprises more than one repair template.

In certain embodiments, the trans-splicing system comprises a nucleic acid guide-binding protein domain comprising a nuclease-inactive CRISPR/Cas system.

In certain embodiments, expression and/or the activity of the trans-splicing system is transient.

“Transient expression” refers to the temporary expression of genes that are expressed for a time after a nucleic acid has been introduced into eukaryotic cells. In some embodiments, transient expression of the trans-splicing system may be controlled with a small molecule. As used herein, the term “small molecule” refers to a non-nucleic acid/non-amino acid molecule. As used herein, the term “small molecule binding domain” refers to a portion of a molecule, often a protein, that specifically binds to a given small molecule. These can include a tet-ON or tet-OFF system or chemogenetic control using synthetic transcription factors and protease inhibitors. For example, dCas13-NLS-NS3-MS2 remains active and uncleaved in the presence of BILN-2061. (Tague *et al.*, *Nature Methods*, Volume 15, pages 519–522 (2018) and Wagner *et al.* *Nature Chemical Biology*, Volume 14, pages 1043–1050 (2018), incorporated by reference herein in their entireties). In some embodiments, transient expression of the

trans-splicing system can be controlled by degradation of the delivery particle. In some embodiments, expression of the trans-splicing system may be controlled with a light-activated transcription factor (Konermann *et al.*, Nature, Volume 500, pages 472–476 (22 August 2013), incorporated by reference herein in its entirety). In some embodiments, assembly of the trans-splicing system may be controlled with a small molecule, *e.g.*, chemically induced dimerization. Examples include, dCas13-NLS-FKBP and FKBP-NLS-MS2, assembled by FK1012; dCas13-NLS-FKBP and CNA-NLS-MS2, assembled by FK506; and dCas13-NLS-FRB and MS2-FKBP transiently assembled by rapamycin, and rapidly disassembled by FK506. (Braun *et al.*, Nature Communications, DOI: 10.1038/s41467-017-00644-y, incorporated by reference herein in its entirety). Additional examples include dCas13-NLS-ABI1 and PYL1-MS2, assembled by abscisic acid (Gao *et al.*, Nature Methods, DOI: <https://doi.org/10.1038/nmeth.4042>, incorporated by reference herein in its entirety). Other examples of small molecules and their chemically induced systems are included in Stanton *et al.* (Science, DOI: <http://dx.doi.org/10.1126/science.aao5902>, incorporated by reference herein in its entirety). In some embodiments, activity of the trans-splicing system can be controlled using a small molecule to degrade the system. In some embodiments, the small molecule binding domain may be linked to the CRISPR system via a self-cleaving peptide. In some embodiments, the self-cleaving peptide is a 2A self-cleaving peptide. Some examples include, but are not limited to, T2A, P2A, E2A, and F2A sequences.

In some embodiments, assembly of the trans-splicing system is mediated by a SunTag (Tanenbaum *et al.*, Cell, 2014, DOI: <https://doi.org/10.1016/j.cell.2014.09.039>). In some embodiments, assembly of the trans-splicing system is mediated by hairpins on the guide RNA, either native or modified, such as the SAM system (Konermann *et al.*, Nature, 2015, DOI: 10.1038/nature14136).

In some embodiments, transient expression is performed by delivering the trans-splicing system as RNA as shown in Hewitt *et al.*, Science Translational Medicine 30 Jan 2019; Vol. 11, Issue 477, eaat9143, incorporated by reference herein in its entirety. In some embodiments, the trans-splicing system assembly can be controlled via light. For example, dCas13-NLS-CRY2 and CIB1-NLS-MS2 are assembled by 466 nm light. (Konermann *et al.* (2013)). In some embodiments, transient expression is performed by delivering the trans-splicing system with an episomal or non-integrating virus. These viruses include Ad5, AAV, HSV-1, or baculovirus. In some embodiments, activity of the trans-splicing system is mediated by conditionally active inteins, such as inteins that undergo protein splicing in the presence of 4-hydroxytamoxifen (4-HT) or other small molecules. In some embodiments, activity of the trans-splicing system is controlled by 4-HT by including a 4-HT sensitive intein into Cas13 at a location that disrupts Cas13 activity until 4-HT mediated protein splicing has taken place, similar to Davis *et al.* (Nature Chemical Biology, 2015, DOI: <https://doi.org/10.1038/nchembio.1793>).

Delivery

In some embodiments, the nucleic acid introduced into the eukaryotic cell is a plasmid DNA or viral vector.

Preferably, delivery is in the form of a vector which may be a viral vectors, such as a lenti- or baculo- or adeno-viral/adeno-associated viral vectors, but other means of delivery are known (such as yeast systems, microvesicles, gene guns/means of attaching vectors to gold nanoparticles) and are provided. The viral vector may be selected from a variety of families/genera of viruses, including, but not limited to Myoviridae, Siphoviridae, Podoviridae, Corticoviridae, Lipothrrixviridae, Poxviridae, Iridoviridae, Adenoviridae, Polyomaviridae, Papillomaviridae, Mimiviridae, Pandoravirus, Salterprovirus, Inoviridae, Microviridae, Parvoviridae, Circoviridae, Hepadnaviridae, Caulimoviridae, Retroviridae, Cystoviridae, Reoviridae, Birnaviridae, Totiviridae, Partitiviridae, Filoviridae, Orthomyxoviridae, Deltavirus, Leviviridae, Picornaviridae, Marnaviridae, Secoviridae, Potyviridae, Caliciviridae, Hepeviridae, Astroviridae, Nodaviridae, Tetraviridae, Luteoviridae, Tombusviridae, Coronaviridae, Arteriviridae, Flaviviridae, Togaviridae, Virgaviridae, Bromoviridae, Tymoviridae, Alphaflexiviridae, Sobemovirus, or Idaeovirus.

A vector may mean not only a viral or yeast system (for instance, where the nucleic acids of interest may be operably linked to and under the control of (in terms of expression, such as to ultimately provide a processed RNA) a promoter), but also direct delivery of nucleic acids into a host cell. While in herein methods the vector may be a viral vector and this is advantageously AAV, other viral vectors as herein discussed can be employed, such as lentivirus. For example, baculoviruses may be used for expression in insect cells. These insect cells may, in turn be useful for producing large quantities of further vectors, such as AAV or lentivirus adapted for delivery of the present invention. Also envisaged is a method of delivering the present CRISPR enzyme comprising delivering to a cell mRNA encoding the CRISPR enzyme. It will be appreciated that in certain embodiments the CRISPR enzyme is truncated, and/or comprised of less than one thousand amino acids or less than four thousand amino acids, and/or is a nuclease or nickase, and/or is codon-optimized, and/or comprises one or more mutations, and/or comprises a chimeric CRISPR enzyme, and/or the other options as herein discussed.

In some embodiments, expression of a nucleic acid sequence encoding a CRISPR enzyme may be driven by a promoter. In some embodiments, a single promoter drives expression of a nucleic acid sequence encoding a CRISPR enzyme and one or more of the guide sequences. In some embodiments, the CRISPR enzyme and guide sequence(s) are operable linked to and expressed from the same promoter. In some embodiments, the CRISPR enzyme and guide sequence(s) are expressed from different promoters. For example, the promoter(s) can be, but are not limited to, a UBC promoter, a PGK promoter, an EF1A promoter, a CMV promoter, an EFS promoter, a SV40 promoter, and a TRE promoter. The promoter may be a weak or a strong promoter. The promoter may be a constitutive promoter or an inducible promoter. In some embodiments, the promoter can

also be an AAV ITR, and can be advantageous for eliminating the need for an additional promoter element, which can take up space in the vector. The additional space freed up by use of an AAV ITR can be used to drive the expression of additional elements, such as guide sequences. In some embodiments, the promoter may be a tissue specific promoter.

5 In some embodiments, an enzyme coding sequence encoding a CRISPR enzyme is codon-optimized for expression in particular cells, such as eukaryotic cells. The eukaryotic cells may be those of or derived from a particular organism, such as a mammal, including but not limited to human, mouse, rat, rabbit, dog, or non-human primate. In general, codon optimization refers to a process of modifying a nucleic acid sequence for enhanced expression in the host cells of interest by replacing at
10 least one codon (e.g., about or more than about 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, or more codons) of the native sequence with codons that are more frequently or most frequently used in the genes of that host cell while maintaining the native amino acid sequence. Various species exhibit particular bias for certain codons of a particular amino acid. Codon bias (differences in codon usage between organisms) often correlates with the efficiency of translation of messenger RNA (mRNA), which is in
15 turn believed to be dependent on, among other things, the properties of the codons being translated and the availability of particular transfer RNA (tRNA) molecules. The predominance of selected tRNAs in a cell is generally a reflection of the codons used most frequently in peptide synthesis. Accordingly, genes can be tailored for optimal gene expression in a given organism based on codon optimization. Codon usage tables are readily available, for example, at the “Codon Usage Database”,
20 and these tables can be adapted in a number of ways. See Nakamura, Y., et al. “codon usage tabulated from the international DNA sequence databases: status for the year 2000” Nucl. Acids Res. 28:292 (2000). Computer algorithms for codon optimizing a particular sequence for expression in a particular host cell are also available, such as Gene Forge (Aptagen; Jacobus, Pa.), are also available. In some embodiments, one or more codons (e.g., 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, or more, or all
25 codons) in a sequence encoding a Cas protein correspond to the most frequently used codon for a particular amino acid.

In some embodiments, a vector encodes a Cas protein comprising one or more nuclear localization sequences (NLSs), such as about or more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more NLSs. In some embodiments, the Cas protein comprises about or more than 1, 2, 3, 4, 5, 6, 7, 8, 9,
30 10, or more NLSs at or near the amino-terminus, about or more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more NLSs at or near the carboxy-terminus, or a combination of these (e.g., one or more NLS at the amino-terminus and one or more NLS at the carboxy terminus). When more than one NLS is present, each may be selected independently of the others, such that a single NLS may be present in more than one copy and/or in combination with one or more other NLSs present in one or more
35 copies. In some embodiments, an NLS is considered near the N- or C-terminus when the nearest amino acid of the NLS is within about 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50, or more amino acids along the polypeptide chain from the N- or C-terminus. Typically, an NLS consists of one or more

short sequences of positively charged lysines or arginines exposed on the protein surface, but other types of NLS are known. In some embodiments, the NLS is between two domains, for example between the Cas13 protein and the viral protein. The NLS may also be between two functional domains separated or flanked by a glycine-serine linker.

5 In general, the one or more NLSs are of sufficient strength to drive accumulation of the Cas protein in a detectable amount in the nucleus of a eukaryotic cell. In general, strength of nuclear localization activity may derive from the number of NLSs in the Cas protein, the particular NLS used, or a combination of these factors. Detection of accumulation in the nucleus may be performed by any suitable technique. For example, a detectable marker may be fused to the Cas protein, such that
10 location within a cell may be visualized, such as in combination with a means for detecting the location of the nucleus (e.g., a stain specific for the nucleus such as DAPI). Examples of detectable markers include fluorescent proteins (such as green fluorescent proteins, or GFP; RFP; CFP), and epitope tags (HA tag, FLAG tag, SNAP tag). Cell nuclei may also be isolated from cells, the contents of which may then be analyzed by any suitable process for detecting protein, such as
15 immunohistochemistry, Western blot, or enzyme activity assay. Accumulation in the nucleus may also be determined indirectly, such as by an assay for the effect of CRISPR complex formation (e.g. assay for DNA cleavage or mutation at the target sequence, or assay for altered gene expression activity affected by CRISPR complex formation and/or CRISPR complex activity), as compared to a control not exposed to the CRISPR complex, or exposed to a Cas protein lacking the one or more
20 NLSs.

In general, a guide sequence is any polynucleotide sequence having sufficient complementarity with a target polynucleotide sequence to hybridize with the target sequence and direct sequence-specific binding of a CRISPR complex to the target sequence. In some embodiments, the degree of complementarity between a guide sequence and its corresponding target sequence, when
25 optimally aligned using a suitable alignment algorithm, is about or more than about 50%, 60%, 75%, 80%, 85%, 90%, 95%, 97.5%, 99%, or more. Optimal alignment may be determined with the use of any suitable algorithm for aligning sequences, non-limiting example of which include the Smith-Waterman algorithm, the Needleman-Wunsch algorithm, algorithms based on the Burrows-Wheeler Transform (e.g., the Burrows Wheeler Aligner), ClustalW, ClustalX, BLAT, Novoalign (Novocraft
30 Technologies, ELAND (Illumina, San Diego, Calif.), SOAP (available at soap.genomics.org.cn), and Maq (available at maq.sourceforge.net). In some embodiments, a guide sequence is about or more than about 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 75, or more nucleotides in length. In some embodiments, a guide sequence is less than about 75, 50, 45, 40, 35, 30, 25, 20, 15, 12, or fewer nucleotides in length. The ability of a guide sequence
35 to direct sequence-specific binding of a CRISPR complex to a target sequence may be assessed by any suitable assay.

In some aspects, the invention provides methods comprising delivering one or more polynucleotides, such as one or more vectors as described herein, one or more transcripts thereof, and/or one or proteins transcribed therefrom, to a host cell. In some aspects, the invention further provides cells produced by such methods, and organisms (such as animals, plants, or fungi) comprising or produced from such cells. In some embodiments, a Cas protein in combination with (and optionally complexed) with a guide sequence is delivered to a cell. Conventional viral and non-viral based gene transfer methods can be used to introduce nucleic acids in mammalian cells or target tissues. Such methods can be used to administer nucleic acids encoding components of a CRISPR system to cells in culture, or in a host organism. Non-viral vector delivery systems include DNA plasmids, RNA (e.g., a transcript of a vector described herein), naked nucleic acid, and nucleic acid complexed with a delivery vehicle, such as a liposome. Viral vector delivery systems include DNA and RNA viruses, which have either episomal or integrated genomes after delivery to the cell. For a review of gene therapy procedures, see Anderson, *Science* 256:808-8313 (1992); Navel and Felgner, *TIBTECH* 11:211-217 (1993); Mitani and Caskey, *TIBTECH* 11:162-166 (1993); Dillon, *TIBTECH* 11:167-175 (1993); Miller, *Nature* 357:455-460 (1992); Van Brunt, *Biotechnology* 6(10):1149-1154 (1988); Vigne, *Restorative Neurology and Neuroscience* 8:35-36 (1995); Kremer and Perricaudet, *British Medical Bulletin* 51(1):31-44 (1995); Haddada et al., in *Current Topics in Microbiology and Immunology*, Doerfler and Bohm (eds) (1995); and Yu et al., *Gene Therapy* 1:13-26 (1994).

The CRISPR/Cas system as described herein, can be delivered using adeno-associated virus (AAV), lentivirus, adenovirus, or other viral vector types, or combinations thereof. Cas protein(s) and one or more guide RNAs can be packaged into one or more viral vectors. In some embodiments, the targeted trans-splicing system is delivered via AAV as a split intein system, similar to Levy *et al.* (*Nature Biomedical Engineering*, 2020, DOI: <https://doi.org/10.1038/s41551-019-0501-5>). In other embodiments, the targeted trans-splicing system can be delivered via AAV as a trans-splicing system, similar to Lai *et al.* (*Nature Biotechnology*, 2005, DOI: 10.1038/nbt1153). In some embodiments, the viral vector is delivered to the tissue of interest by, for example, an intramuscular injection, while other times the viral delivery is via intravenous, transdermal, intranasal, oral, mucosal, intrathecal, intracranial or other delivery methods. Such delivery may be either via a single dose, or multiple doses. One skilled in the art understands that the actual dosage to be delivered herein may vary greatly depending upon a variety of factors, such as the vector chosen, the target cell, organism, or tissue, the general condition of the subject to be treated, the degree of transformation/modification sought, the administration route, the administration mode, the type of transformation/modification sought, etc.

The use of RNA or DNA viral based systems for the delivery of nucleic acids takes advantage of highly evolved processes for targeting a virus to specific cells in the body and trafficking the viral payload to the nucleus. Viral vectors can be administered directly to patients (in vivo) or they can be used to treat cells in vitro, and the modified cells may optionally be administered to patients (ex vivo).

Conventional viral based systems could include retroviral, lentivirus, adenoviral, adeno-associated and herpes simplex virus vectors for gene transfer. Integration in the host genome is possible with the retrovirus, lentivirus, and adeno-associated virus gene transfer methods, often resulting in long term expression of the inserted transgene. Additionally, high transduction efficiencies have been observed in many different cell types and target tissues. Viral-mediated in vivo delivery of Cas13 and guide RNA provides a rapid and powerful technology for achieving precise mRNA perturbations within cells, especially in post-mitotic cells and tissues.

In certain embodiments, delivery of the trans-splicing system to a cell is viral. In certain embodiments, the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus, or baculovirus.

In certain embodiments, delivery of the trans-splicing system to a cell is non-viral. In certain embodiments, the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, transfection through membrane disruption using mechanical shear forces, mechanical transfection, and nanoparticle delivery.

Preferably, the vector is a viral vector, such as a lenti-, baculo-, or adeno-viral/adeno-associated viral vectors, but other means of delivery are known (such as yeast systems, microvesicles, gene guns/means of attaching vectors to gold nanoparticles) and are provided. In some embodiments, one or more of the viral or plasmid vectors may be delivered via liposomes, nanoparticles, exosomes, microvesicles, or a gene-gun.

Lentiviruses are complex retroviruses that have the ability to infect and express their genes in both mitotic and post-mitotic cells. The most commonly known lentivirus is the human immunodeficiency virus (HIV), which uses the envelope glycoproteins of other viruses to target a broad range of cell types.

In another embodiment, minimal non-primate lentiviral vectors based on the equine infectious anemia virus (EIAV) are also contemplated, especially for ocular gene therapy (see, e.g., Balagaan, J gene Med 2006: 8:275-285, Published online 21 November 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jgm.845). In another embodiment, RetinoStat, an equine infectious anemia virus-based lentiviral gene therapy vector that expresses angiostatic proteins endostatin and angiostatin that is delivered via a subretinal injection for the treatment of the wet form of age-related macular degeneration is also contemplated (see, e.g., Binley et al., HUMAN GENE THERAPY 23:980-991 (September 2012)) may be modified for the CRISPR-Cas system of the present invention.

Lentiviral vectors have been disclosed as in the treatment for Parkinson's Disease, see, e.g., US Patent Publication No. 20120295960 and US Patent Nos. 7,303,910 and 7,351,585. Lentiviral vectors have also been disclosed for delivery to the brain, see, e.g., US Patent Publication Nos. US20110293571, US20040013648; US20070025970, US20090111106, and US Patent No. 7,259,015.

Methods of non-viral delivery of nucleic acids include lipofection, nucleofection, microinjection, biolistics, virosomes, liposomes, immunoliposomes, polycation or lipid:nucleic acid conjugates, naked DNA, artificial virions, and agent-enhanced uptake of DNA. Lipofection is described in e.g., U.S. Pat. Nos. 5,049,386; 4,946,787; and 4,897,355; and lipofection reagents are sold commercially (e.g., Transfectam™ and Lipofectin™). Cationic and neutral lipids that are suitable for efficient receptor-recognition lipofection of polynucleotides include those of Felgner, WO 91/17424; WO 91/16024. Delivery can be to cells (e.g., in vitro or ex vivo administration) or target tissues (e.g., in vivo administration).

The preparation of lipid:nucleic acid complexes, including targeted liposomes such as immunolipid complexes, is well known to one of skill in the art (see, e.g., Crystal, Science 270:404-410 (1995); Blaese et al., Cancer Gene Ther. 2:291-297 (1995); Behr et al., Bioconjugate Chem. 5:382-289 (1994); Remy et al., Bioconjugate Chem. 5:647-654 (1994); Gao et al., Gene Therapy 2:710-722 (1995); Ahmad et al., Cancer Res. 52:4817-4820 (1992); U.S. Pat. Nos. 4,186,183; 4,217,344; 4,235,871; 4,261,975; 4,485,054; 4,501,728; 4,774,085; 4,837,028; and 4,946,787).

In some embodiments, a host cell is transiently or non-transiently transfected with one or more vectors described herein. In some embodiments, a cell is transfected as it naturally occurs in a subject. In some embodiments, a cell that is transfected is taken from a subject. In some embodiments, the cell is derived from cells taken from a subject, such as a cell line. Cell lines are available from a variety of sources known to those with skill in the art (see, e.g., the American Type Culture Collection (ATCC) (Manassas, VA)). In some embodiments, a cell transfected with one or more vectors described herein is used to establish a new cell line comprising one or more vector-derived sequences. In some embodiments, a cell transiently transfected with the components of a CRISPR system as described herein (such as by transient transfection of one or more vectors, or transfection with RNA), and modified through the activity of a CRISPR complex, is used to establish a new cell line comprising cells containing the modification but lacking any other exogenous sequence. In some embodiments, cells transiently or non-transiently transfected with one or more vectors described herein, or cell lines derived from such cells are used in assessing one or more test compounds.

In some embodiments, one or more vectors described herein are used to produce a non-human transgenic animal or transgenic plant. In some embodiments, the transgenic animal is a mammal, such as a mouse, rat, or rabbit. In certain embodiments, the organism or subject is a plant. In certain embodiments, the organism or subject or plant is algae. Methods for producing transgenic plants and animals are known in the art, and generally begin with a method of cell transfection, such as described herein.

In one aspect, the invention provides for methods of modifying a target polynucleotide in a eukaryotic cell. In some embodiments, the method comprises allowing a CRISPR complex to bind to the target polynucleotide to effect cleavage of said target polynucleotide thereby modifying the target

polynucleotide, wherein the CRISPR complex comprises a CRISPR enzyme complexed with a guide sequence hybridized to a target sequence within said target polynucleotide, wherein said guide sequence is linked to a tracer mate sequence which in turn hybridizes to a tracer sequence.

With recent advances in crop genomics, the ability to use CRISPR/Cas systems to perform efficient and cost effective gene editing and manipulation will allow the rapid selection and comparison of single and multiplexed genetic manipulations to transform such genomes for improved production and enhanced traits. In this regard, reference is made to US patents and publications: U.S. Pat. No. 6,603,061 – Agrobacterium-Mediated Plant Transformation Method; U.S. Pat. No. 7,868,149 – Plant Genome Sequences and Uses Thereof and US 2009/0100536 – Transgenic Plants with Enhanced Agronomic Traits, all the contents and disclosure of each of which are herein incorporated by reference in their entirety. In the practice of the invention, the contents and disclosure of Morell et al “Crop genomics: advances and application” Nat Rev Genet. 2011 Dec 29; 13(2):85-96 are also herein incorporated by reference in their entirety.

Any components of the instant CRISPR/Cas system can be delivered in the form of RNA. Cas and/or viral protein mRNA can be generated using *in vitro* transcription. For example, Cas mRNA can be synthesized using a PCR cassette containing the following elements: T7 promoter-Kozak sequence (GCCACC)-Cas13-3' UTR from beta globin-polyA tail (a string of 120 or more adenines). The cassette can be used for transcription by T7 polymerase. Guide RNAs can also be transcribed using *in vitro* transcription from a cassette containing T7 promoter-GG-guide RNA sequence.

The components of the instant CRISPR/Cas system may be delivered simultaneously using nanoparticles or lipid envelopes. For example, Su X, Fricke J, Kavanaugh DG, Irvine DJ (“*In vitro* and *in vivo* mRNA delivery using lipid-enveloped pH-responsive polymer nanoparticles” Mole Phar. 2011 Jun 6; 8(3):774-87. doi: 10.1021/mp100390w. Epub 2011 Apr 1) describes biodegradable core-shell structured nanoparticles with a poly(β -amino ester) (PBAE) core enveloped by a phospholipid bilayer shell. These were developed for *in vivo* mRNA delivery. The pH-responsive PBAE component was chosen to promote endosome disruption, while the lipid surface layer was selected to minimize toxicity of the polycation core. Such are, therefore, preferred for delivering RNA of the present invention.

In one embodiment, nanoparticles based on self-assembling bioadhesive polymers are contemplated, which may be applied to oral delivery of peptides, intravenous delivery of peptides and nasal delivery of peptides, all to the brain. Other embodiments, such as oral absorption and ocular delivery of hydrophobic drugs are also contemplated. The molecular envelope technology involves an engineered polymer envelope which is protected and delivered to the site of the disease (see, e.g., Mazza, M. et al. ACSNano, 2013. 7(2):1016-1026; Siew, A., et al. Mol Pharm, 2012. 9(1):14-28; Lalatsa, A., et al. J Contr Rel, 2012. 161(2):523-36; Lalatsa, A., et al., Mol Pharm, 2012. 9(6):1665-80; Lalatsa, A., et al. Mol Phar, 2012. 9(6):1764-74; Garrett, N.L., et al. J. Biophotonics, 2012.

5(56):458-68; Garrett, N.L., et al. J Raman Spect, 2012. 43(5):681-688; Ahmad, S., et al. J Royal Soc Interface 2010. 7:S423-33; Uchegbu, I.F. Expert Opin Drug Deliv, 2006. 3(5):629-40; Qu, X., et al. Biomacromolecules, 2006. 7(12):3452-9 and Uchegbu, I.F., et al. Int J Pharm, 2001. 224:185-199). Doses of about 5 mg/kg are contemplated, with single or multiple doses, depending on the target tissue.

US Patent Application 20110293703 relates to lipidoid compounds are also particularly useful in the administration of polynucleotides, which may be applied to deliver the CRISPR/Cas system of the present invention. In one aspect, the aminoalcohol lipidoid compounds are combined with an agent to be delivered to a cell or a subject to form microparticles, nanoparticles, liposomes, or micelles. The agent to be delivered by the particles, liposomes, or micelles may be in the form of a gas, liquid, or solid, and the agent may be a polynucleotide, protein, peptide, or small molecule. The aminoalcohol lipidoid compounds may be combined with other aminoalcohol lipidoid compounds, polymers (synthetic or natural), surfactants, cholesterol, carbohydrates, proteins, lipids, etc. to form the particles. These particles may then optionally be combined with a pharmaceutical excipient to form a pharmaceutical composition.

US Patent Application 20130302401 relates to a class of poly(beta-amino alcohols) (PBAs) has been prepared using combinatorial polymerization. The inventive PBAs may be used in biotechnology and biomedical applications as coatings (such as coatings of films or multilayer films for medical devices or implants), additives, materials, excipients, non-biofueling agents, micropatterning agents, and cellular encapsulation agents. When used as surface coatings, these PBAs elicited different levels of inflammation, both in vitro and in vivo, depending on their chemical structures. The large chemical diversity of this class of materials allowed us to identify polymer coatings that inhibit macrophage activation in vitro. Furthermore, these coatings reduce the recruitment of inflammatory cells, and reduce fibrosis, following the subcutaneous implantation of carboxylated polystyrene microparticles. These polymers may be used to form polyelectrolyte complex capsules for cell encapsulation. The invention may also have many other biological applications such as antimicrobial coatings, DNA or siRNA delivery, and stem cell tissue engineering. The teachings of US Patent Application No. 20130302401 may be applied to the CRISPR/Cas system of the present invention.

In another embodiment, lipid nanoparticles (LNPs) are contemplated, In particular, an antitransthyretin small interfering RNA encapsulated in lipid nanoparticles (see, e.g., Coelho et al., N Engl J Med 2013; 369:819-29) may be applied to the CRISPR/Cas system of the present invention.

The charge of the LNP must be taken into consideration. As cationic lipids combined with negatively charged lipids to induce nonbilayer structures that facilitate intracellular delivery. Because charged LNPs are rapidly cleared from circulation following intravenous injection, ionizable cationic lipids with pKa values below 7 were developed (see, e.g., Rosin et al, Molecular therapy, vol. 19, no. 12, pages 1286-2200, Dec. 2011). Negatively charged polymers such as siRNA oligonucleotides may

be loaded into LNPs at low pH values (e.g., pH 4) where the ionizable lipids display a positive charge. However, at physiological pH values, the LNPs exhibit a low surface charge compatible with longer circulation times. Four species of ionizable cationic lipids have been focused upon, namely 1,2-dilinoyleoyl-3-dimethylammonium-propane (DLinDAP), 1,2-dilinoleyloxy-3-N,N-dimethylaminopropane (DLinDMA), 1,2-dilinoleyloxy-keto-N,N-dimethyl-3-aminopropane (DLinKDMA), and 1,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLinKC2-DMA).

Self-assembling nanoparticles with siRNA may be constructed with polyethyleneimine (PEI) that is PEGylated with an Arg-Gly-Asp (RGD) peptide ligand attached at the distal end of the polyethylene glycol (PEG), for example, as a means to target tumor neovasculature expressing integrins and used to deliver siRNA inhibiting vascular endothelial growth factor receptor-2 (VEGFR2) expression and thereby tumor angiogenesis (see, e.g., Schiffelers et al., *Nucleic Acids Research*, 2004, Vol. 32, No. 19). Nanoplexes may be prepared by mixing equal volumes of aqueous solutions of cationic polymer and nucleic acid to give a net molar excess of ionizable nitrogen (polymer) to phosphate (nucleic acid) over the range of 2 to 6. The electrostatic interactions between cationic polymers and nucleic acid resulted in the formation of polyplexes with average particle size distribution of about 100 nm, hence referred to her as nanoplexes.

Exosomes are endogenous nano-vesicles that transport RNAs and proteins which can deliver short interfering (si)RNA to the brain in mice. To reduce immunogenicity, Alvarez-Erviti et al. (2011, *Nat Biotechnol* 29: 341) used self-derived dendritic cells for exosome production.

In certain embodiments, the invention provides a method of treating or inhibiting a condition caused by a defect in a target sequence in a mRNA of interest in a subject (e.g., mammal or human) or a non-human subject (e.g., mammal) in need thereof comprising modifying the subject or a non-human subject by manipulation of the target sequence and wherein the condition is susceptible to treatment or inhibition by manipulation of the target sequence comprising providing treatment comprising: delivering a non-naturally occurring or engineered composition comprising an AAV or lentivirus vector system comprising one or more AAV or lentivirus vectors operably encoding a composition for expression thereof, wherein the target sequence is manipulated by the composition when expressed, wherein the composition comprises: (A) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising a targeted trans-splicing system comprising a non-natural nucleic acid guide-binding protein domain, a nucleic acid guide, a specific RNA-binding domain, and a repair template comprising a splice donor and/or splice acceptor and an RNA sequence that hybridizes under stringent conditions to the specific RNA-binding domain.

Targeting of Cells

The work herein supports the use of CRISPR/Cas systems to target pre-mRNA in post-mitotic cells through delivery of the CRISPR/Cas system to the appropriate location (i.e., to cells within the organs or tissues of interest) to mediate trans-splicing events to pre-mRNA.

5 In certain embodiments, the CRISPR/Cas system further comprises a cell. In certain embodiments, the CRISPR/Cas system is targeted to RNA. In certain embodiments, the CRISPR/Cas system is associated with RNA in the cell. In certain embodiments, the RNA is a pre-mRNA. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA at intron-exon junctions. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA at
10 exon-intron junctions. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at the 3' end of the pre-mRNA. Examples of a sequence targeting the 3' end of a pre-mRNA may include, but is not limited to SEQ ID NO: 70, as disclosed herein. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA within the 3' untranslated region (UTR). Trans-splicing within the 3' UTR can lead to stronger translation of the
15 resulting mRNA. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at an internal site within a pre-mRNA. Examples of a sequence targeting an internal site within a pre-mRNA may include, but is not limited to SEQ ID NO: 92, as disclosed herein. In various embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA within the 5' untranslated region (UTR). The 3' and 5' UTRs of mRNA are known to contain multiple regulatory
20 elements and are critical for the stability and translation of mRNA into protein. Warren *et al.* (Cell Stem Cell, Volume 7, pages 618-630 (2010), incorporated by reference herein in its entirety) used an artificial 5' UTR containing a strong Kozak translation signal and the alpha globin 3' UTR to improve protein production during reprogramming of fibroblasts to induced pluripotent stem cells. In certain embodiments, the CRISPR/Cas system can mediate trans-splicing to provide a 3'UTR sequence to
25 change the strength of translation, in some cases leading to stronger translation and significant increases in protein production. For example, 3' UTRs from genes including, but are not limited to, AGXT, ALB, APOA2, ASL, C3, CYP2E1, FBA, HPX, and/or ORM, can be used to change the strength of translation. Also, for example, 5' UTRs from genes including, but are not limited to, AGXT, ALB, APOA2, ASL, C3, CYP2E1, FBA, HPX, and/or ORM, can be used to change the
30 strength of translation.

In certain embodiments, the CRISPR/Cas system is associated with DNA in the cell. In certain embodiments, the CRISPR/Cas system is not associated with DNA in the cell.

In certain embodiments, the trans-splicing system is introduced into the cell. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of a cell.
35 In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of a cell. In another aspect of the invention, provided herein is a method of mediating a targeted trans-splicing event on a pre-mRNA in a cell, the method comprising introducing a targeted

trans-splicing CRISPR/Cas system into the cell, wherein the system comprises a nuclease-inactive nucleic acid-targeting CRISPR/Cas system, a nucleic acid guide that specifically hybridizes to a nucleic acid locus of interest, a specific RNA-binding domain, and a repair template comprising an RNA sequence that hybridizes under stringent conditions to the specific-RNA-binding domain.

5 Gene editing using Type II, and more recently Type V, CRISPR systems can be accomplished through either of two pathways: non-homologous end joining (NHEJ) or homology-directed repair (HDR). NHEJ does not require the cells to be actively dividing, however HDR is only active in dividing cells. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of the cell. In certain embodiments, the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell. The cell can be a dividing cell, or a post-mitotic cell. In certain embodiments, the post-mitotic cell can be simply one or post-mitotic cells, or an organ per se or a tissue within it. In certain embodiments, the post-mitotic cell can be selected from the group consisting of a neuron, myocyte, and adipocyte. The post-mitotic cells may be comprised within a vertebrate animal, either a patient (in the sense of an animal in need of trans-splicing mediated treatment) or a model organism, or may be in cell culture, an organoid, or other ex vivo tissue, such a “liver on a chip” for instance where hepatocytes are seeded and grown on a scaffold. With the development of 3-D printing techniques being applied to biology, printed tissues are within grasp and it is entirely feasible that liver cells or tissues printed in this way to create an organoid or onto a chip could also be targeted. Non-liver alternatives are also envisaged, particularly for other post-mitotic cells/tissues.

 Thus, provided is a model organism comprising post-mitotic cells, such as neurons or kidney cells, to which the present CRISPR-Cas system has been delivered. Such collections may include post-mitotic organs, organoids, or cells populating a scaffold (‘kidney on a chip’).

 In particular, such post-mitotic cells may express, or comprise polynucleotides capable of expressing, a Cas enzyme. As discussed herein, this has the advantage of providing a ready model for interrogating gene product function through targeted-trans-splicing of pre-mRNA. This is particularly useful in studying conditions of the post-mitotic cells, such as the kidney or brain, such as those listed herein, as well as broader conditions such as obesity.

 Also provided is a method of inducing transcript perturbation in one or more post-mitotic cells, comprising transducing population of cells with a CRISPR/Cas system according to the present invention to thereby alter transcripts of a population of cells. The method may be *ex vivo* or *in vitro*, for instance in a cell culture or in an *ex vivo* or *in vitro* model (such as an organoid). Alternatively, the method may be *in vivo*, in which case it may also include isolating a population of cells from the subject, and transplanting the population of cells (back) into the subject. Transcript perturbation may be for one or more, or two or more, or three or more, or four or more genes. However, if the cells already comprise Cas, whether expressed as a protein or encoded by polynucleotides already comprised within the cells, then only the CRISPR polynucleotide needs to be delivered. The method

may include extraction from and, optionally, re-insertion back into the post-mitotic cell. By delivering, it is meant actually physical delivery of the polynucleotides to the nucleus of the cell, but also transection. Therefore, delivery should also be read as including transfection unless otherwise apparent.

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Gene Therapy

Because the described invention can be used to mediate trans-splicing in a non-dividing cell, in certain embodiments the cell is in a subject suffering from a disease or disorder. In certain embodiments the disease or disorder is a neurodegenerative, neurological, or neuromuscular disease or disorder. In certain embodiments, the disease or disorder is selected from the group consisting of spinal muscular atrophy, Rett Syndrome, Angelman syndrome, Parkinson's disease, Alzheimer's disease, Huntington's disease, frontotemporal dementia, lysosomal storage diseases, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).

The approaches taken herein demonstrate that the instant invention can be applied to gene therapy. For instance, correction of one or more deficient genotypes (for example single point mutations) is achievable through the use of the present CRISPR-Cas system in the post-mitotic cells discussed herein. Monogenic conditions associated with the post-mitotic are particularly preferred and are exemplified herein.

Although one guide may be used, so-called multiplexing with two, three, four or more guides, is particularly useful in gene therapy where multiple defective genotypes are to be corrected (either multiple errors in a single gene or multiple errors spread across several genes).

Accordingly, in certain embodiments the invention provides a method of modifying post-mitotic cells of an organism, e.g., mammal including a human or a non-human mammal or organism by manipulation of a target sequence in a genomic locus of interest comprising delivering a non-naturally occurring or engineered composition comprising a viral or plasmid vector system comprising one or more viral or plasmid vectors operably encoding a composition for expression thereof, wherein the composition comprises: (A) a non-naturally occurring or engineered composition comprising a vector system comprising one or more vectors comprising a targeted trans-splicing system comprising a non-natural nucleic acid guide-binding protein domain, a nucleic acid guide, a specific RNA-binding domain, and a repair template comprising a splice donor and/or splice acceptor and an RNA sequence that hybridizes under stringent conditions to the specific RNA-binding domain.

The trans-splicing system as described herein can be used to interrogate the function of one or more genes in post-mitotic cells. This may be achieved through delivery and expression of the CRISPR/Cas system to the post-mitotic cell, wherein the guide(s) of the CRISPR/Cas system are designed to recruit the CRISPR/Cas system to the pre-mRNA target or targets of interest. Equally, where the CRISPR/Cas is already comprised within the post-mitotic cell, protein (transcribed) form, then delivery of the guides to the post-mitotic cell will suffice. Having a CRISPR/Cas system induced

by a small molecule may be advantageous here. Where the CRISPR/Cas is already within the post-mitotic cell, in polynucleotide (untranscribed), then delivery of the guides to the post-mitotic cell as well as induction of transcription of the Cas9 polynucleotide will be necessary. Having the CRISPR/Cas system under the control of an inducible or repressible promoter, such as the tet (tetracycline) on-off system may be advantageous here.

One aspect that is particularly promising is the integration of CRISPR techniques with phenotypic assays to determine the phenotypic changes, if any, resulting from gene perturbations, especially knock downs. Use of the CRISPR/Cas system can be combined with biochemical, sequencing, electrophysiological, and behavioral analysis to study the function of the targeted genomic element.

This, in one aspect, there is provided a method of interrogating the function of one or more genes in a post-mitotic cell, comprising inducing an expression of a modulated mRNA and determining changes in phenotype due to one or more genes in the condition thereby interrogating the function of the one or more proteins translated from the modulated pre-mRNA.

The following applies broadly to appropriate aspects of the invention. The cell may be in a subject, such as a human, animal, or model organism, so that protein function is interrogated *in vivo*. however, it is also envisaged that the cell may be *ex vivo*, for instance in a cell culture or in a model organ or organoid. In some embodiments, the method may include isolation of a first population of cells from the subject, optionally culturing them and transducing them with one or more CRISPR/Cas systems. Further optional culturing may follow. Transplantation of the transduced cells back into the subject may then occur.

The cell may be from any of the tissues or organism described herein. The brain is one preferred example, providing for said method of interrogating the function of one or more gene products, such as pre-mRNA, wherein the post-mitotic cell is a brain cell, for instance a neuron. Particularly *in vivo*, this allows for the interrogation of mutated or modified protein function on animal behavior. The animal is preferably a mammal, for instance a rodent. Given the complexity of the nervous system, which consists of intricate networks of heterogeneous cell types, being able to efficiently edit pre-mRNAs of neurons *in vivo* enables direct testing of gene function in relevant cell types embedded in native contexts.

Kits

The present disclosure provides kits for carrying out a method. In one aspect, the invention provides kits containing any one or more of the elements disclosed in the above methods and compositions. In some embodiments, the kit comprises a vector system and instructions for using the kit. In some embodiments, the kit comprises a vector system comprising regulatory elements and polynucleotides encoding the CRISPR/Cas trans-splicing system. In some embodiments, the kit comprises a viral delivery system of the CRISPR/Cas trans-splicing system. In some embodiments,

the kit comprises a non-viral delivery system of the CRISPR/Cas trans-splicing system. Elements may be provided individually or in combinations, and may be provided in any suitable container, such as a vial, a bottle, or a tube. In some embodiments, the kit includes instruction in one or more languages, for examples, in more than one language.

5 In some embodiments, a kit comprises one or more reagents for use in a process utilizing one or more of the elements described herein. Reagents may be provided in any suitable container. For example, a kit may provide one or more reaction or storage buffers. Reagents may be provided in a form that is usable in a particular assay, or in a form that requires addition of one or more other components before use (e.g. in concentrate or lyophilized form). A buffer can be any buffer, including
10 but not limited to a sodium carbonate buffer, a sodium bicarbonate buffer, a borate buffer, a Tris buffer, a MOPS buffer, a HEPES buffer, and combinations thereof. In some embodiments, the buffer is alkaline. In some embodiments, the buffer has a pH from about 7 to about 10. In some embodiments, the kit comprises one or more oligonucleotides corresponding to a guide sequence for insertion into a vector so as to operably link the guide sequence and a regulatory element.

15 The invention is further described in detail by reference to the following experimental examples. These examples are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variation which become evident as a result of the teaching
20 provided herein.

EXAMPLES

Example 1 – Engineering of the CRISPR-based trans-splicing system

A CRISPR-based trans-splicing system was engineered to comprise a guide RNA, such as a guide RNA (gRNA), an exon or a group of exons of interest conjugated to an engineered intron with
25 ms2 hairpins, and a catalytically inactive Cas13b (dCas13b) linked to a MS2 binding protein (**FIG. 1A**). Assembly of the trans-splicing system relies on the dCas13b recognizing the gRNA scaffold, and the MS2 binding protein recognizing the ms2 hairpins of the engineered intron (**FIG. 1B**). Instead of inducing a cis-splicing reaction (**FIG. 1C**), the CRISPR-dCas13b system induces a trans-splicing event similar to the endogenous spliceosome-based reaction that is illustrated in **FIG. 1D**. In
30 the CRISPR/Cas-based system, the trans-splicing event occurs when the above described CRISPR-dCas13b assembly binds to a pre-mRNA. When the dCas13b that is linked to a MS2 binding protein binds to the pre-mRNA, the cis-splice acceptor is blocked. The MS2 binding protein tethers a trans-splicing RNA molecule of interest, and with the binding of the dCas13b to the target pre-mRNA, directs the trans-splicing RNA to the pre-mRNA. This enables highly efficient trans-splicing (**FIG.**
35 **1E**).

Several DNA constructs were utilized to reduce CRISPR-mediated trans-splicing to practice (FIG. 2A). First, a U6 promoter-driven gRNA construct with a *Prevotella sp.* Cas13b (PspCas13b) RNA scaffold was used to drive expression of the gRNA in the cells. The dCas13b was linked to a MS2 binding protein via a SV40 nuclear localization signal (SV40 NLS) and glycine-serine linker. Bovine growth hormone polyadenylation signal (bGHpA) was used to allow for stable expression of the construct. A splice donor was used to generate expression of a pre-mRNA that could be assayed for trans-splicing. Blue fluorescent protein (BFP) was used as a marker to validate expression of the splice donor, and a self-cleaving p2A linker was used on truncated GFP (5' GFP). To ensure the splice acceptor would undergo trans-splicing, Matrix Metalloproteinase 9 (MMP9) intron 1 and exon 2 were placed downstream, followed by bGHpA to ensure stable expression. A splice acceptor reporter was designed, such that trans-splicing would generate a complete GFP, which could be observed by flow cytometry. The designed ms2 intron consists of i) a binding domain (BD) which hybridizes to MMP9 intron 1 in the splice donor reporter, ii) two ms2 loops, iii) a branch point (BP), and iv) a polypyrimidine tract (PPT), followed by v) a splice acceptor sequence. The second half of the truncated GFP was placed behind the ms2 intron, which was then followed by a reverse transcription primer binding site (RT), allowing for generation of next generation sequencing libraries (NGS) to validate trans-splicing via RNAseq. To confirm expression of the splice acceptor reporter, an internal ribosome entry site (IRES) was used to drive translation of mCherry, thus allowing mCherry measurement via flow cytometry independent of trans-splicing. Lastly, a ms2 null ($\Delta 2 \times$ ms2) splice acceptor reporter was used to measure the effect of ms2 loops on CRISPR-mediated trans-splicing efficiency.

Upon successful trans-splicing, the truncated GFP exons (5' GFP, 3' GFP) introduced by the splice donor and acceptor reporters are spliced together, generating a transcript that contains a complete GFP mRNA sequence capable of creating a functional GFP protein product (FIG. 2B). Cells were gated for BFP+ and mCherry+ using flow cytometry, to validate expression of both the splice donor (SD) and splice acceptor (SA) reporters respectively. From the gated double positive BFP+ mCherry+ population, trans-splicing activity was measured by the fraction of cells that were GFP+.

Example 2 – Measuring CRISPR-mediated trans-splicing

HEK293FT cells were transfected in a 12-well plate format, with a total of 1250 ng of DNA and 4 μ L of Lipofectamine 2000 per condition. Each construct was one fourth of the total DNA transfection, with the exception of pUC19, which was used as non-coding control DNA in conditions where less than four components were delivered. A total of 1250 ng of DNA was delivered. Media was changed 6 hours post-transfection, and the cells were analyzed via flow cytometry 48 hours after transfection. Negative controls (columns 1-5 of FIG. 3A) showed no detection of trans-splicing via the GFP reporter assay. Column 6, which represents the state-of-the-art for trans-splicing, led to

detection of trans-splicing in $0.69\% \pm 0.08\%$ (mean $\pm$ SD, $n = 4$) of BFP+ mCherry+ cells. CRISPR-mediated trans-splicing (column 11) led to detection of trans-splicing in $19.58\% \pm 1.01\%$ (mean $\pm$ SD, $n = 4$) of BFP+ mCherry+ cells, which was a 28.03 ± 1.45 -fold increase. As expected, CRISPR-mediated trans-splicing had a significant decrease in efficiency when utilizing the ms2 null ($\Delta 2x$ ms2) SA reporter (column 12). Interestingly, there was a significant increase in trans-splicing compared to the case where dCas13b-MS2 and a gRNA were not expressed (column 6) by 2.45 ± 0.45 -fold ($p = 0.00074$), suggesting that binding dCas13b to the SA prevents cis-splicing, thereby promoting trans-splicing in contexts where there are no further exons for cis-splicing.

RNAseq libraries were created by carrying out reverse transcription on the SA reporter using a reverse transcription primer that binds to the RT site on the SA reporter mRNA. The RT site was designed to also carry a TruSeq adapter sequence, such that read 1 of the final library would be the 3' end of GFP. The read 2 sequencing adapter was randomly inserted via tagmentation. Reads were filtered by having read 1 match the 3' end of GFP. Read 2 was then aligned using BWA to a whole transcriptome reference concatenated with the SD and SA reporters. The on-target fraction (plotted) was calculated by dividing the number of reads that map to the SD reporter by the number of total reads that align to the transcriptome (including the SD reporter) but do not align to the SA reporter (FIG. 3B).

Example 3 – Generation of RNAseq library to measure on-target trans-splicing

RNAseq libraries generated by RT of the SA reporter were analyzed for mapping position of read 2. As expected, read 2 showed high mapping to the exonic region of the SD reporter, demonstrating trans-splicing. In contrast, only 1 read mapped to the MMP9 intron and MMP9 exon 2, which was likely from index-hopping or chimeric events (FIG. 4A).

To validate cis-splicing of the SD reporter, RNAseq libraries were generated by reverse transcription of the poly(A) tail. As expected, cis-splicing was observed as the number of reads was lower for the intronic region (MMP intron 1) and higher for the exonic regions (BFP-2A-5'GFP and MMP9 exon 2) (FIG. 4B).

To better understand the gRNA design constraints for CRISPR-mediated trans-splicing, several gRNAs were designed to target different regions of the SD reporter. gRNAs-1-4 targeted the SA site, while gRNAs 5 and 6 targeted the intron. gRNAs 7 and 8 targeted MMP9 exon 2, while gRNAs 9 and 10 targeted bGHpA. gRNAs 11 and 12 targeted BFP in the first exon (FIG. 5).

Targeted trans-splicing was measured by using the truncated GFP trans-splicing reporter assay. Flow cytometry was conducted on transfected cells with 3 biological replicates per condition. When using a gRNA that targets the splice acceptor site, CRISPR-mediated trans-splicing improved trans-splicing efficiency by ~50-fold with a gRNA designed to target the splice acceptor site. In this case, the most effective gRNA (gRNA 4) has 3' guide mapping to the splice acceptor site. As

expected, targeting the CRISPR system to alternative regions of the SD reporter result in marginal gains in trans-splicing efficiency (**FIG. 6A**).

Fold-increases in targeted trans-splicing are marginal when excluding dCas13b-MS2, as measured by the truncated GFP trans-splicing reporter assay (**FIG. 6B**). Flow cytometry was conducted on transfected cells with three biological replicates per condition.

Example 4 – Trans-splicing induced by a small molecule

In order to test if the trans-splicing dCas13b complex could be modified to induce trans-splicing with a small molecule, dCas13b was fused to ABI1, and the MS2 was fused to PYL1, both via glycine-serine linkers (**FIG. 8A**). It was hypothesized that with this architecture, trans-splicing can be transiently induced via introduction of abscisic acid (ABA), as the machinery assembles in the presence of ABA. The construct delivered by a single expression cassette was a CMV-dPspCas13b-ABI1-2A-PYL1-MS2. A split GFP reporter was utilized to assay trans-splicing activity via GFP measurement through flow cytometry.

Using the construct as described above, the split GFP reporter was trans-spliced in the presence of 1.5 mM ABA, resulting in >40% of cells being GFP+ (**FIG. 8B**). HEK293FT cells were transfected using Lipofectamine 2000 per the manufacturer's instructions, and flow cytometry was conducted 72 hours after transfection. ABA was titrated across multiple samples, and 3 biological replicates per ABA concentration were measured via flow cytometry. To demonstrate that ABA could control the induced targeted trans-splicing, a split GFP reporter was trans-spliced in the presence of ABA, and the fold-change in GFP translation was tightly controlled by ABA concentration (**FIG. 8C**).

Example 5 – Measuring trans-splicing at splice junctions

To measure exon junctions, full-length RNAseq was conducted on 293FT cells transfected with dCas13b-MS2, gRNA, and the split GFP reporter system (SD reporter, SA reporter with 2x ms2). Cells were gated for BFP+ and mCherry+ via flow cytometry, to validate expression of both the splice donor (SD) and splice acceptor (SA) reporters respectively, and were then sorted into TCL buffer to lyse the cells prior to RNAseq library construction. RNAseq reads spanning all possible junctions were filtered using regular expressions, and were subsequently mapped onto all possible junction sequences, namely, trans-spliced junctions (TS), cis-spliced junctions (CS), and non-spliced junctions (NS). The mapping positions were the plotted to illustrate reads spanning possible junctions (**FIG. 9A**).

Full length RNAseq reads spanning all possible junctions were filtered using regular expressions, and were subsequently mapped onto all possible junction sequences, namely, the trans-spliced junction (TS), cis-spliced junction (CS), and non-spliced junction (NS). A fraction of spliced reads that were trans-spliced were calculated and plotted for all transfection conditions (**FIG. 9B**).

Full length RNAseq reads spanning all possible junctions were filtered using regular expressions, and were subsequently mapped onto all possible junction sequences, namely the TS, CS, and NS as above. Fractions of the spliced reads that were cis-spliced was calculated and plotted for all transfection conditions (**FIG. 9C**). Results show that the reporter undergoes efficient splicing, and that dCas13 inhibits cis-splicing in the presence of a targeting gRNA.

Example 6 – Strategies for targeted trans-splicing

FIG. 10A illustrates a strategy for 5' targeting of trans-splicing. For this strategy, a dCas13b-MS2 or analogue, can be targeted to a splice donor (SD), while simultaneously providing a 5' repair template for 5' correction or modification of RNA. Such a strategy may be advantageous when the correction or modification is near the 5' end of the mRNA. **FIG. 10B** illustrates an internal targeted trans-splicing strategy. A dCas13b-MS2 or analogue, can be targeted both to a splice acceptor, and a splice donor, while simultaneously providing a repair template with an exon, or group of exons, possessing both a splice acceptor and splice donor. **FIG. 10C** illustrates a strategy for 3' targeting of trans-splicing. For this strategy, a 3' repair template may be provided for 3' correction or modification of RNA, along with a dCas13b-MS2, or analogue, targeting a splice acceptor (SA). Such a strategy may be advantageous when the correction or modification is near the 3' end of the mRNA.

Example 7 – Internal Exon Repair

FIG. 11A illustrates a construct to be used for internal exon repair. Standard gRNA constructs were used, along with CMV-dPspCas13b-MS2 to test whether internal exon repair is possible with CRISPR-mediated trans-splicing. GFP was split into three exons, and GFP exons 1 and 3 were utilized in the target RNA molecule design. To simulate a pathogenic exon, MMP9 exon 2 was placed between GFP exons 1 and 3 on the target molecule, along with corresponding flanking introns: MMP9 intron 1 and MMP9 intron 2. The internal repair template was designed to have GFP exon 2 flanked by two synthetic introns, each with an ms2 hairpin.

FIG. 11B illustrates an assay for monitoring internal exon repair. The target transcript is monitored via expression of blue fluorescent protein (BFP). Cells expressing the target transcript are GFP negative, as the middle exon of GFP (GFP exon 2) is missing from the transcript. Upon internal exon repair, GFP exon 2 from the repair template is trans-spliced in order to create a complete GFP mRNA, and the BFP moiety is lost via the T2A self cleaving peptide. The presence of GFP mRNA leads to translation and expression of GFP protein, which can be measured through flow cytometry.

FIG. 11C is a readout of GFP expression following internal exon repair. 293FT cells were transfected using lipofectamine 2000 per manufacturer's instructions and cells were transfected in a 96 well format (100 ng per well) with four biological replicates for each condition. Flow cytometry was conducted 48 hours after transfection. Several gRNAs targeting the splice donor (SD) were designed (SD targeting gRNAs 1-5), and delivered in conjunction with a splice acceptor (SA)

targeting gRNA. In the absence of gRNAs, no GFP⁺ cells were detected. However, upon introduction of gRNAs, GFP⁺ cells were detected and the fraction of GFP⁺ cells varied depending on the placement of the gRNA relative to the splice donor.

5 Example 8 – Use of Cas13 Orthologs

To test whether Cas13d could also lead to CRISPR-mediated trans-splicing, dRfxCas13d was benchmarked against dPspCas13b. Four guides were designed for RfxCas13d, which all targeted the splice acceptor site in the target reporter. MS2 was fused to the N and C-terminus in two different Cas13d architectures. 293FT cells were transfected using lipofectamine 2000 per manufacturer's instructions and cells were transfected in a 96 well format (100 ng per well) with three biological replicates per condition. Flow cytometry was conducted 48 hours after transfection, and cells were gated on BFP and mCherry in order to only consider cells with both target and repair template reporters. BFP+mCherry⁺ cells were gated on GFP to determine trans-splicing frequency. Mild trans-splicing was observed in the RfxCas13d systems, which were far outperformed by the PspCas13b system (FIG. 12).

Example 9 – AAV-Based Delivery of CRISPR Trans-Splicing System

To test whether the CRISPR system could be delivered with a multi-vector AAV-based approach, individual components were cloned into constructs with AAV2 ITRs to enable AAV packaging. AAV2/8 was produced in 293FT cells by PEI co-transfecting each transfer vector with Rep2/Cap8 (pAAV2/8) and AAV helper plasmid (pAdDeltaF6) in a 3:5:6 ratio at 30 ug of DNA per 150 mm dish. Media was changed 24 hours after transfection, and supernatants were harvested 72 hours after transfection. Supernatant was then filtered with a 0.45 um cellulose acetate filter and AAV was concentrated by using a 100kDa MWCO amicon filter at 4000 rcf for 30 minutes at 4C. 293FT cells were then transduced in suspension using 3 uL of AAV per well in a 96 well plate with four biological replicates per condition. Flow cytometry was conducted 72 hours after AAV transduction in order to measure CRISPR-mediated trans-splicing. Cells were gated on BFP and mCherry in order to only consider cells with both target and repair template reporters. BFP+mCherry⁺ cells were gated on GFP to determine trans-splicing frequency. Delivery of the CRISPR system via a multi-vector AAV approach showed significant increase in trans-sicing as measured by GFP⁺ fluorescence in flow cytometry (FIG. 13).

CLAIMS

1. A targeted trans-splicing system comprising:
 - a nucleic acid-targeting CRISPR/Cas system;
 - a nucleic acid guide;
 - a specific RNA-binding domain; and
 - a repair template comprising a splice donor and/or acceptor and an RNA sequence that hybridizes under physiological conditions to the specific RNA-binding domain.
2. The targeted trans-splicing system of claim 1, wherein the nucleic acid guide is a RNA guide.
3. The targeted trans-splicing system of claim 1, wherein the nucleic acid guide is a DNA guide.
4. The targeted trans-splicing system of any one of claims 1-3, wherein the trans-splicing system comprises one nucleic acid guide.
5. The targeted trans-splicing system of any one of claims 1-3, wherein the trans-splicing system comprises more than one nucleic acid guide.
6. The targeted trans-splicing system of claim 5, wherein the nucleic acid guides recognize multiple targets.
7. The targeted trans-splicing system of any one of claims 1-6, wherein the nucleic acid guide targets a splice acceptor (SA) site.
8. The targeted trans-splicing system of any one of claims 1-6, wherein the nucleic acid guide targets a splice donor (SD) site.
9. The targeted trans-splicing system of any one of claims 1-8, wherein the nucleic acid guide targets a region near a splice site.
10. The targeted trans-splicing system of any one of claims 1-9, wherein the nucleic acid guide targets a region within 200 nucleotides of a splice site.

11. The targeted trans-splicing system of any one of claims 1-10, wherein the nucleic acid guide targets a region less than or equal to 100 nucleotides from a splice site.
- 12.. The targeted trans-splicing system of any one of claims 1-11, wherein the more than one nucleic acid guides target one nucleic acid of interest.
13. The targeted trans-splicing system of any one of claims 1-11, wherein the more than one nucleic acid guides target multiple nucleic acids of interest.
14. The targeted trans-splicing system of claim 1, wherein the CRISPR/Cas system comprises a Cas13 polypeptide.
15. The targeted trans-splicing system of claim 14, wherein the Cas13 is a nuclease-inactive Cas13 polypeptide (dCas13).
16. The targeted trans-splicing system of claim 14, wherein the Cas13 is a nuclease-active Cas13 polypeptide.
17. The targeted trans-splicing system of any one of claims 1-16, wherein the specific RNA-binding domain comprises a viral protein.
18. The targeted trans-splicing system of claim 17, wherein the viral protein is a MS2 binding protein.
19. The targeted trans-splicing system of claim 17, **wherein the viral protein is a λ N protein.**
20. The targeted trans-splicing system of claim 17, wherein the viral protein is a PP7 coat protein.
21. The targeted trans-splicing system of claim 17, wherein the viral protein is a QBeta coat protein.

22. The targeted trans-splicing system of any one of claims 17-21, wherein the viral protein is covalently bound to the CRISPR/Cas system.
23. The targeted trans-splicing system of any one of claims 17-21, wherein the viral protein is not covalently bound to the CRISPR/Cas system.
24. The targeted trans-splicing system of any one of claims 17-21, wherein the viral protein and CRISPR/Cas system is a fusion protein.
25. The targeted trans-splicing system of any one of claims 1-24, wherein the trans-splicing system comprises one repair template.
26. The targeted trans-splicing system of any one of claims 1-24, wherein the trans-splicing system comprises more than one repair template.
27. The targeted trans-splicing system of claim 25 or 26, wherein the repair template is introduced as DNA.
28. The targeted trans-splicing system of claim 25 or 26, wherein the repair template is delivered as RNA.
29. The targeted trans-splicing system of any one of claims 25-28, wherein the repair template is expressed as RNA.
30. The targeted trans-splicing system of any one of claims 25-29, wherein the repair template comprises a splice acceptor.
31. The targeted trans-splicing system of any one of claims 25-29, wherein the repair template comprises a splice donor.
32. The targeted trans-splicing system of any one of claims 25-31, wherein the repair template comprises one or more splice sites.

33. The targeted trans-splicing system of any one of claims 25-32, wherein the repair template comprises an exon.
34. The targeted trans-splicing system of any one of claims 25-33, wherein the repair template comprises more than one exon.
35. The targeted trans-splicing system of any one of claims 25-34, wherein the repair template comprises an intron.
36. The targeted trans-splicing system of any one of claims 25-35, wherein the repair template comprises more than one intron.
37. The targeted trans-splicing system of any one of claims 25-36, wherein the repair template comprises one or multiple sequences that hybridize to the target nucleic acid of interest.
38. The targeted trans-splicing system of any one of claims 25-37, wherein at least one portion of the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein.
39. The targeted trans-splicing system of any one of claims 25-37, wherein the repair **template comprises a boxB hairpin that specifically binds to the λ N protein.**
40. The targeted trans-splicing system of any one of claims 25-37, wherein the repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein.
41. The targeted trans-splicing system of any one of claims 25-37, wherein the repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.
42. The targeted trans-splicing system of any one of claims 1-41, further comprising a cell.
43. The targeted trans-splicing system of claim 42, wherein at least one portion of the trans-splicing system is introduced into the cell.

44. The targeted trans-splicing system of any one of claim 42 or 43, wherein expression and/or activity of at least one portion of the trans-splicing system is transient.
45. The targeted trans-splicing system of claim 44, wherein the activity of at least one portion of the trans-splicing system is regulated by a small molecule.
46. The targeted trans-splicing system of claim 45, wherein the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903/AP, and Auxin.
47. The targeted trans-splicing system of any one of claims 43-46 wherein the at least one portion is a Cas13 protein.
48. The targeted trans-splicing system of claim 47, wherein the Cas13 protein further comprises a small molecule binding domain.
49. The targeted trans-splicing system of claim 48, wherein the Cas13 protein and the small molecule binding domain are linked by a glycine-serine linker.
50. The targeted trans-splicing system of claim 45-49, wherein the small molecule binding domain is an ABA-binding domain.
51. The targeted trans-splicing system of claim 50, wherein the ABA-binding domain comprises an ABI1 polypeptide.
52. The targeted trans-splicing system of claim 45, further comprising a viral protein.
53. The targeted trans-splicing system of claim 52, wherein the viral protein further comprises a small molecule binding domain.
54. The targeted trans-splicing system of claim 52 or 53, wherein the viral protein and the small molecule binding domain are linked by a glycine-serine linker.

55. The targeted trans-splicing system of claims 53 or 54, wherein the small molecule binding domain is an ABA-binding domain.
56. The targeted trans-splicing system of claim 55, wherein the ABA-binding domain comprises a PYL1 polypeptide.
57. The targeted trans-splicing system of claim 56, wherein the addition of ABA induces targeted trans-splicing of a target pre-mRNA.
58. The targeted trans-splicing system of any one of claims 42-57, wherein delivery of at least one portion of the trans-splicing system to the cell is viral.
59. The targeted trans-splicing system of claim 58, wherein the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus, or baculovirus.
60. The targeted trans-splicing system of claims 42-57, wherein delivery of at least one portion of the trans-splicing system to a cell is non-viral.
61. The targeting trans-splicing system of claim 60, wherein the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.
62. The targeted trans-splicing system of any one of claims 1-61, wherein the CRISPR/Cas system is targeted to a nucleic acid.
63. The targeted trans-splicing system of claim 62, wherein the nucleic acid is RNA.
64. The targeted trans-splicing system of claim 62, wherein the nucleic acid is DNA.
65. The targeted trans-splicing system of any one of claims 1-64, wherein the CRISPR/Cas system is associated with RNA in the cell.
66. The targeted trans-splicing system of claim 65, wherein the RNA is a pre-mRNA.

67. The targeted trans-splicing system of any one of claims 1-64, wherein the CRISPR/Cas system is associated with DNA in the cell.
68. The targeted trans-splicing system of any one of claims 1-64, wherein the CRISPR/Cas system is not associated with DNA in the cell.
69. The targeted trans-splicing system of any one of claims 1-68, wherein the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of the cell.
70. The targeted trans-splicing system of any one of claims 1-69, wherein the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell.
71. The targeted trans-splicing system of any one of claims 1-70, wherein the trans-splicing occurs in dividing cells.
72. The targeted trans-splicing system of any one of claims 1-70, wherein the trans-splicing occurs in post-mitotic cells.
73. The targeted trans-splicing system of claim 72, wherein post-mitotic cells are neurons, myocytes, or adipocytes.
74. The targeted trans-splicing system of any one of claims 1-73, wherein expression of at least one portion of the trans-splicing system is inducible.
75. The targeted trans-splicing system of any one of claims 1-73, wherein activity of at least one portion of the trans-splicing system is inducible.
76. A method of mediating a targeted trans-splicing event on a pre-mRNA in a cell, the method comprising introducing at least one portion of a targeted trans-splicing CRISPR/Cas system into the cell, wherein the CRISPR/Cas system comprises;
- a nucleic acid-targeting CRISPR/Cas system;
 - a nucleic acid guide that specifically hybridizes to a nucleic acid locus of interest;
 - a specific RNA-binding domain; and

a repair template comprising a splice donor and/or a splice acceptor and an RNA sequence that hybridizes under physiological conditions to the specific RNA-binding domain.

77. The method of claim 76, wherein the nucleic acid guide comprises RNA.
78. The method of claim 76, wherein the nucleic acid guide comprises DNA.
79. The method of claim 76, wherein a single nucleic acid guide is introduced into the cell.
80. The method of claim 76, wherein multiple nucleic acid guides are introduced into the cell.
81. The method of claim 80, wherein the multiple nucleic acid guides target one nucleic acid of interest.
82. The method of claim 81, wherein the multiple nucleic acid guides target more than one nucleic acid of interest.
83. The method of any one of claims 76-82, wherein the nucleic acid guide targets a splice acceptor (SA) site.
84. The method of any one of claims 76-82, wherein the nucleic acid guide targets a splice donor (SD) site.
85. The method of any one of claims 76-84, wherein the nucleic acid guide targets a region near the splice site.
86. The method of any one of claims 76-85, wherein the nucleic acid guide targets a region within 200 nucleotides of the splice site.
87. The method of any one of claims 76-86, wherein the nucleic acid guide targets a region less than or equal to 100 nucleotides of the splice site.

88. The method of claim 76 wherein a plurality of nucleic acid guides is delivered to a plurality of cells.
89. The method of claim 76, wherein the CRISPR/Cas system comprises a Cas13 polypeptide.
90. The method of claim 89, wherein the Cas13 polypeptide is a Cas13b polypeptide.
91. The method of claim 90, wherein the Cas13b polypeptide is a nuclease-inactive Cas13b (dCas13b).
92. The method of claim 90, wherein the Cas13b polypeptide is a nuclease-active Cas13b.
93. The method of claims 76-92, wherein the specific RNA-binding domain comprises a viral protein.
94. The method of claim 93, wherein the viral protein is a MS2 binding protein.
95. The method of claim 93, **wherein the viral protein is a λ N protein.**
96. The method of claim 93, wherein the viral protein is a PP7 coat protein.
97. The method of claim 93, wherein the viral protein is a QBeta coat protein.
98. The method of any one of claims 93-97, wherein the viral protein is covalently bound to the CRISPR/Cas system.
99. The method of any one of claims 93-97, wherein the viral protein is not covalently bound to the CRISPR/Cas system.
100. The method of any one of claims 93-97, wherein the viral protein and CRISPR/Cas system is a fusion protein.

101. The method of claim 76, wherein the trans-splicing system comprises one splice acceptor repair template.
102. The method of claim 76, wherein the trans-splicing system comprises more than one splice acceptor repair template.
103. The method of claim 76, wherein the trans-splicing system comprises one splice donor repair template.
104. The method of claim 76, wherein the trans-splicing system comprising more than one splice donor repair template.
105. The method of any one of claims 101-104, wherein the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein.
106. The method of any one of claims 101-104, wherein the repair template comprises a **boxB hairpin that specifically binds to the λ N protein.**
107. The method of any one of claims 101-104, wherein the repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein.
108. The method of any one of claims 101-104, wherein the repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.
109. The method of any one of claims 76-108, wherein expression of at least one portion of the trans-splicing system is transient.
110. The method of any one of claims 76-108, wherein the activity of at least one portion of the trans-splicing system is transient.
111. The method of claims 109 or 110, wherein the activity of at least one portion of the trans-splicing system is regulated by a small molecule.

112. The method of claim 111, wherein the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, Cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903/AP20187, and Auxin.
113. The method of claim 112, wherein at least one portion of the trans-splicing system comprises a Cas13 polypeptide.
114. The method of claim 113, wherein the Cas13 polypeptide further comprises a small molecule binding domain.
115. The method of claim 114, wherein the Cas13 polypeptide and the small molecule binding domain are linked by a glycine-serine linker.
116. The method of claim 114 or 115, wherein the small molecule binding domain is an ABA-binding domain.
117. The method of claim 116, wherein the ABA-binding domain comprises an ABI1 polypeptide.
118. The method of claim 111, further comprising a viral protein.
119. The method of claim 118, wherein the viral protein further comprises a small molecule binding domain.
120. The method of claim 119, wherein the viral protein and the small molecule binding domain are linked by a glycine-serine linker.
121. The method of claims 119 or 120, wherein the small molecule binding domain is an ABA-binding domain.
122. The method of claim 121, wherein the ABA-binding domain comprises a PYL1 polypeptide.

123. The method of claim 122, wherein the addition of ABA induces targeted trans-splicing of a target pre-mRNA.

124. The method of any one of claims 76-123, wherein delivery of at least one portion of the trans-splicing system to a cell is viral.

125. The method of claim 124, wherein the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus or baculovirus.

126. The method of any one of claims 76-122, wherein delivery of at least one portion of the trans-splicing system to a cell is non-viral.

127. The method of claim 126, wherein the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.

128. The method of any one of claims 76-127, wherein the CRISPR/Cas system associates with RNA in the cell.

129. The method of claim 128, wherein the RNA is a pre-mRNA.

130. The method of any one of claims 76-129, wherein the CRISPR/Cas system associates with DNA in the cell.

131. The method of any one of claims 76-129, wherein the CRISPR/Cas system does not associate with DNA in the cell.

132. The method of claims 76-129, wherein the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the nucleus of the cell.

133. The method of claims 76-129, wherein the CRISPR/Cas system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell.

134. The method of claims 132 or 133, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at intron-exon junctions.

135. The method of claims 132 or 133, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at exon-intron junctions.

136. The method of any one of claims 76-135, wherein the splice repair template does not comprise a splice acceptor.

137. The method of any one of claims 76-135, wherein the splice repair template does not comprise a splice donor.

138. The method of any one of claims 76-135, wherein the splice repair template comprises both a splice acceptor and a splice donor.

139. The method of any one of claims 76-138, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at the 5' end of the pre-mRNA.

140. The method of any one of claims 76-138, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at the 3' end of the pre-mRNA.

141. The method of any one of claims 76-138, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA at an internal site within a pre-mRNA.

142. The method of any one of claims 76-138, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA within the 3' untranslated region (UTR).

143. The method of any one of claims 76-138, wherein the CRISPR/Cas system mediates trans-splicing of a pre-mRNA within the 5' untranslated region (UTR).

144. The method of any of claims 76-143, wherein the cell is a dividing cell.

145. The method of any of claims 76-143, wherein the cell is a post-mitotic cell.

146. The method of claim 145, wherein the post-mitotic cell is selected from the group consisting of a neuron, myocyte, and adipocyte.
147. The method of any one of claims 76-146, wherein expression of at least one portion of the trans-splicing system is inducible .
148. The method of any one of claims 76-146, wherein activity of at least one portion of the trans-splicing system is inducible.
149. The method of any one of claims 144-146, wherein the cell is in a subject suffering from a disease or disorder.
150. The method of claim 149, wherein the disease or disorder is a neurodegenerative, neurological, or neuromuscular disease or disorder.
151. The method of claim 150, wherein the neurodegenerative, neurological, or neuromuscular disease or disorder is selected from the group consisting of spinal muscular atrophy, Rett Syndrome, Angelman syndrome, Parkinson's disease, Alzheimer's disease, Huntington's disease, frontotemporal dementia, lysosomal storage diseases, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).
152. A targeted trans-splicing system comprising:
a nucleic acid binding protein domain;
a specific RNA-binding domain; and
a repair template comprising a splice donor and/or a splice acceptor and an RNA sequence that hybridizes under stringent conditions to the specific RNA-binding domain.
153. The targeted trans-splicing system of claim 152, wherein the nucleic acid binding protein domain targets a splice acceptor (SA) site.
154. The targeted trans-splicing system of claim 152, wherein the nucleic acid binding protein domain targets a splice donor (SD) site.

155. The targeted trans-splicing system of any one of claims 152-154, wherein the specific RNA-binding domain comprises a viral protein.

156. The targeted trans-splicing system of claim 155, wherein the viral protein is a MS2 binding protein.

157. The targeted trans-splicing system of claim 155, wherein the viral protein is a λ N protein.

158. The targeted trans-splicing system of claim 155, wherein the viral protein is a PP7 coat protein.

159. The targeted trans-splicing system of claim 155, wherein the viral protein is a QBeta coat protein.

160. The targeted trans-splicing system of any one of claims 155-159, wherein the viral protein is covalently bound to the nucleic acid binding protein domain.

161. The targeted trans-splicing system of any one of claims 155-159, wherein the viral protein is not covalently bound to the nucleic acid binding protein domain.

162. The targeted trans-splicing system of any one of claims 155-159, wherein the viral protein and nucleic acid binding protein domain is a fusion protein.

163. The targeted trans-splicing system of claim 152, wherein the trans-splicing system comprises one splice acceptor repair template.

164. The targeted trans-splicing system of claim 152, wherein the trans-splicing system comprises more than one splice acceptor repair template.

165. The targeted trans-splicing system of claim 152, wherein the trans-splicing system comprises one splice donor repair template.

166. The targeted trans-splicing system of claim 152, wherein the trans-splicing system comprises more than one splice donor repair template.

167. The targeted trans-splicing system of claim 152, wherein the trans-splicing system comprises a repair template comprising a splice donor and/or a splice acceptor.

168. The targeted trans-splicing system of claim 163-167, wherein at least one portion of the repair template comprises a ms2 hairpin that specifically binds to the MS2 binding protein.

169. The targeted trans-splicing system of claim 163-167, wherein the splice repair template comprises a boxB hairpin that specifically binds to the λ N protein.

170. The targeted trans-splicing system of claim 163-167, wherein the splice repair template comprises a PP7 hairpin that specifically binds to the PP7 coat protein.

171. The targeted trans-splicing system of claim 163-167, wherein the splice repair template comprises a QBeta hairpin that specifically binds to the QBeta coat protein.

172. The targeted trans-splicing system of any one of claims 152-171, further comprising a cell.

173. The targeted trans-splicing system of claim 172, wherein at least one portion of the trans-splicing system is introduced into the cell.

174. The targeted trans-splicing system of any one of claim 172 or 173, wherein expression and/or activity of at least one portion of the trans-splicing system is transient.

175. The targeted trans-splicing system of claim 174, wherein the activity of at least one portion of the trans-splicing system is regulated by a small molecule.

176. The targeted trans-splicing system of claim 175, wherein the small molecule is selected from abscisic acid (ABA), rapamycin (or rapalog), FK506, Cyclosporine A, FK1012, Gibberellin3-AM, FKCsA, AP1903/AP20187, and Auxin.

177. The targeted trans-splicing system of claim 174, wherein at least one portion is the nucleic acid binding protein domain.

178. The targeted trans-splicing system of claim 177, wherein the nucleic acid binding protein domain further comprises a small molecule binding domain.

179. The targeted trans-splicing system of claim 178, wherein the nucleic acid binding protein domain and the small molecule binding domain are linked by a glycine-serine linker.

180. The targeted trans-splicing system of claim 178 or 179, wherein the small molecule binding domain is an ABA-binding domain.

181. The targeted trans-splicing system of claim 180, wherein the ABA-binding domain comprises an ABI1 polypeptide.

182. The targeted trans-splicing system of claim 174, wherein at least one portion is the viral protein.

183. The targeted trans-splicing system of claim 182, wherein the viral protein further comprises a small molecule binding domain.

184. The targeted trans-splicing system of claim 182 or 183, wherein the viral protein and the small molecule binding domain are linked by a glycine-serine linker.

185. The targeted trans-splicing system of claim 184, wherein the small molecule binding domain is an ABA-binding domain.

186. The targeted trans-splicing system of claim 185, wherein the ABA-binding domain comprises a PYL1 polypeptide.

187. The targeted trans-splicing system of claim 186, wherein the addition of ABA induces targeted trans-splicing of a target pre-mRNA.

188. The targeted trans-splicing system of any one of claims 172-187, wherein delivery of at least one portion of the trans-splicing system to the cell is viral.

189. The targeted trans-splicing system of claim 188, wherein the virus is a retrovirus, adenovirus, adeno-associated virus, herpes simplex virus, anellovirus, or baculovirus.

190. The targeted trans-splicing system of any one of claims 172-187, wherein delivery of at least one portion of the trans-splicing system to a cell is non-viral.

191. The targeting trans-splicing system of claim 190, wherein the non-viral delivery system is selected from a cationic lipid vehicle, electroporation, calcium phosphate transfection, mechanical transfection, and nanoparticle delivery.

192. The targeted trans-splicing system of any one of claims 152-191, wherein the nucleic acid binding protein domain is targeted to DNA.

193. The targeted trans-splicing system of any one of claims 152-191, wherein the nucleic acid binding protein domain is targeted to RNA.

194. The targeted trans-splicing system of any one of claims 152-193, wherein the nucleic acid binding protein domain is associated with RNA in the cell.

195. The targeted trans-splicing system of claim 194, wherein the RNA is a pre-mRNA.

196. The targeted trans-splicing system of any one of claims 152-192, wherein the nucleic acid binding protein domain is associated with DNA in the cell.

197. The targeted trans-splicing system of any one of claims 152-192, wherein the nucleic acid binding protein domain is not associated with DNA in the cell.

198. The targeted trans-splicing system of any one of claims 152-197, wherein the system mediates trans-splicing of pre-mRNA in the nucleus of the cell.

199. The targeted trans-splicing system of any one of claims 152-197, wherein the system mediates trans-splicing of pre-mRNA in the cytoplasm of the cell.

200. The targeted trans-splicing system of claims 198 or 199, wherein the system mediates trans-splicing of a pre-mRNA at intron-exon junctions.

201. The targeted trans-splicing system of claims 198 or 199 wherein the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA at exon-intron junctions.

202. The targeted trans-splicing system of any one of claims 152-201, wherein the splice repair template does not comprise a splice donor.

203. The targeted trans-splicing system of any one of claims 152-201, wherein the splice repair template does not comprise a splice acceptor.

204. The targeted trans-splicing system of any one of claims 152-201, wherein the splice repair template comprises both a splice acceptor and a splice donor.

205. The targeted trans-splicing system of any one of claims 152-204, wherein the system comprises multiple splice templates.

206. The targeted trans-splicing system of any one of claims 152-205, wherein the multiple splice templates comprise splice repair templates that comprise a splice acceptor and splice repair templates that comprise a splice donor.

207. The targeted trans-splicing system of claim 206, wherein at least some of the multiple splice repair templates comprise a splice acceptor and a splice donor.

208. The targeted trans-splicing system of any one of claims 152-207, wherein the system mediates trans-splicing of a pre-mRNA at the 5' end of the pre-mRNA.

209. The targeted trans-splicing system of any one of claims 152-207, wherein the system mediates trans-splicing of a pre-mRNA at the 3' end of the pre-mRNA.

210. The targeted trans-splicing system of any one of claims 152-207 wherein the system mediates trans-splicing of a pre-mRNA at an internal site within a pre-mRNA.

211. The targeted trans-splicing system of any one of claims 152-210, wherein the system replaces the 5' or the 3' end of the target mRNA.

212. The targeted trans-splicing system of any one of claims 208-211, wherein the target mRNA is a pre-mRNA.

213. The targeted trans-splicing system of any one of claims 152-212, wherein the system comprises replacing one or more exons of the target mRNA, excluding the first and last exon of the target mRNA.

214. The targeted trans-splicing system of any one of claims 152-213, wherein the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA within the 3' untranslated region (UTR).

215. The targeted trans-splicing system of any one of claims 152-213, wherein the nucleic acid binding protein domain mediates trans-splicing of a pre-mRNA within the 5' untranslated region (UTR).

216. The targeted trans-splicing system of any one of claims 152-215, wherein the trans-splicing occurs in dividing cells.

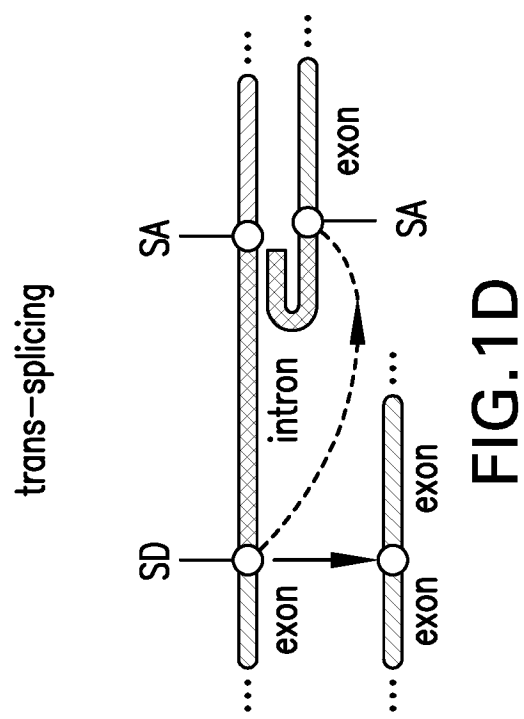
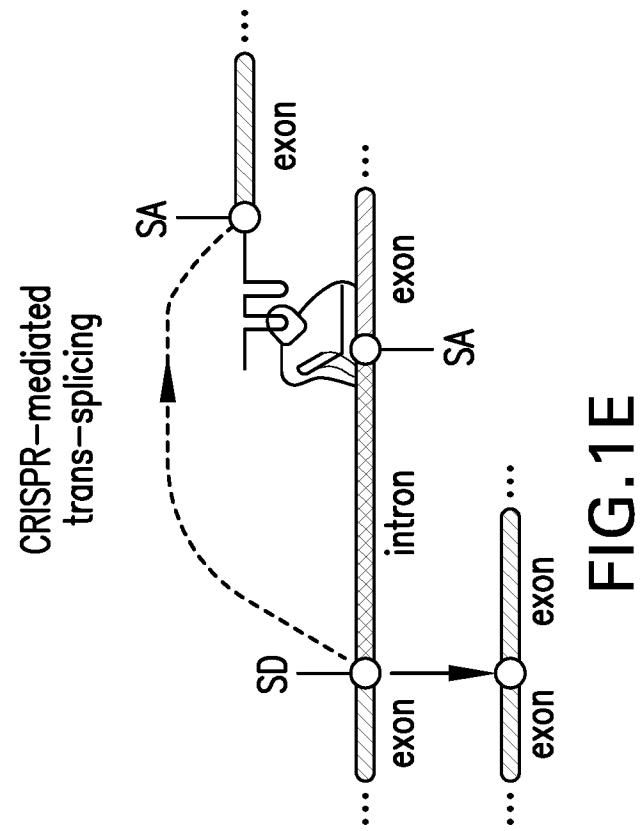
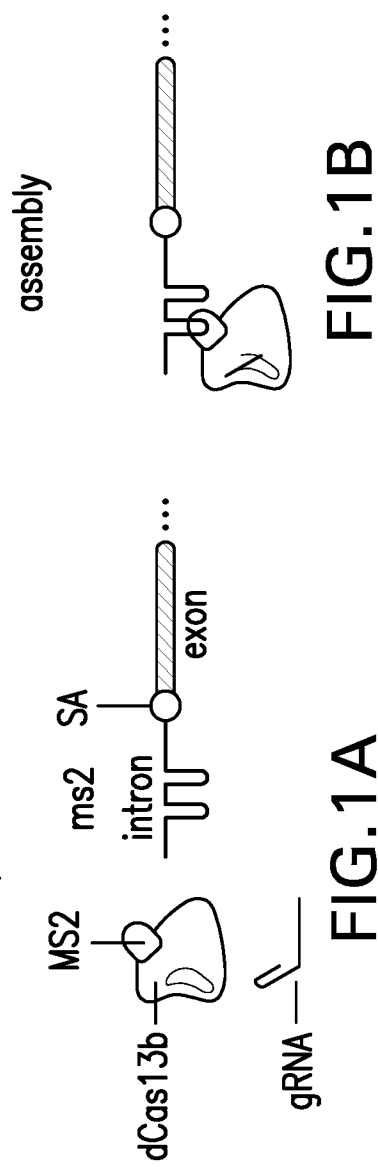
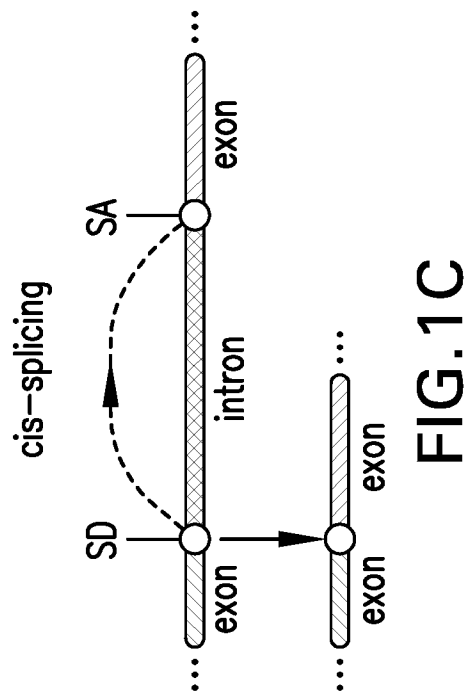
217. The targeted trans-splicing system of any one of claims 152-215, wherein the trans-splicing occurs in post-mitotic cells.

218. The targeted trans-splicing system of claim 217, wherein the post-mitotic cells are neurons, myocytes, or adipocytes.

219. The targeted trans-splicing system of any one of claims 152-218, wherein expression of at least one portion of the trans-splicing system is inducible.

220. The targeted trans-splicing system of any one of claims 152-218, wherein activity of at least one portion of the trans-splicing system is inducible.

221. The targeted trans-splicing system of any one of claims 152-220, wherein the nucleic acid binding protein domain is a domain from a zinc finger nuclease (ZFNs) or a Pumby module, or is an RNA recognition motif.



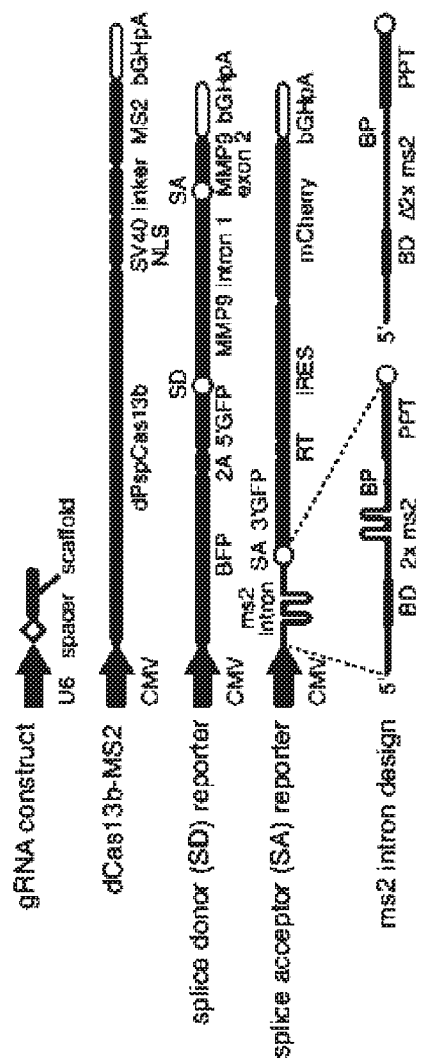


FIG. 2A

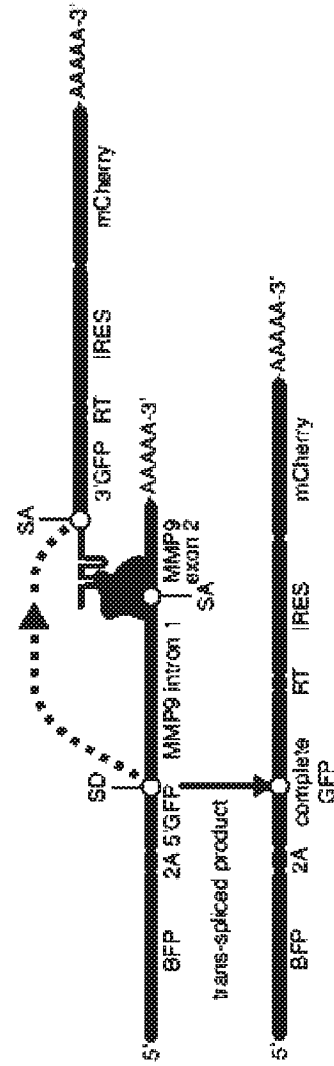


FIG. 2B

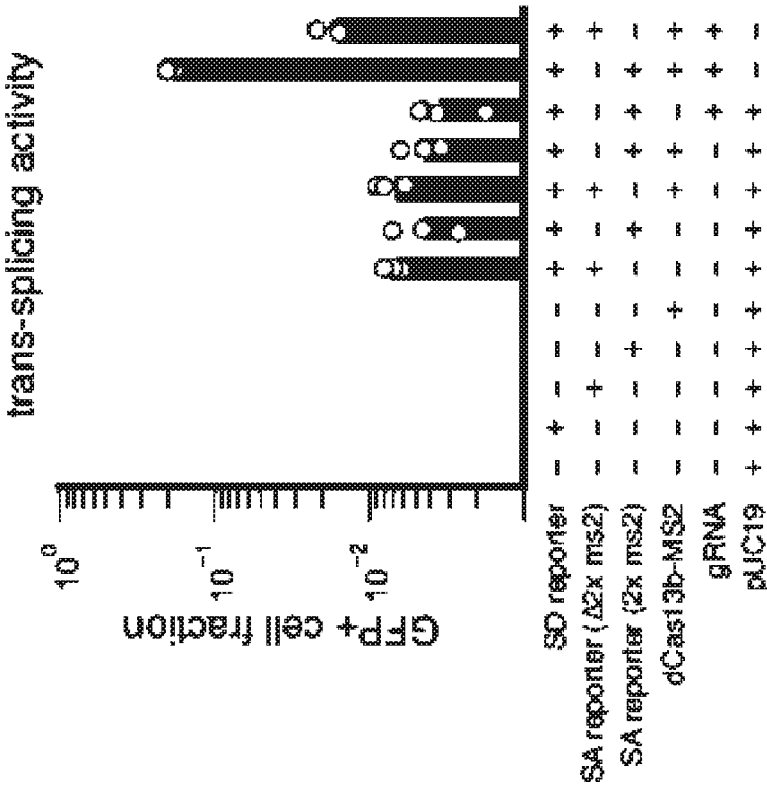


FIG. 3A

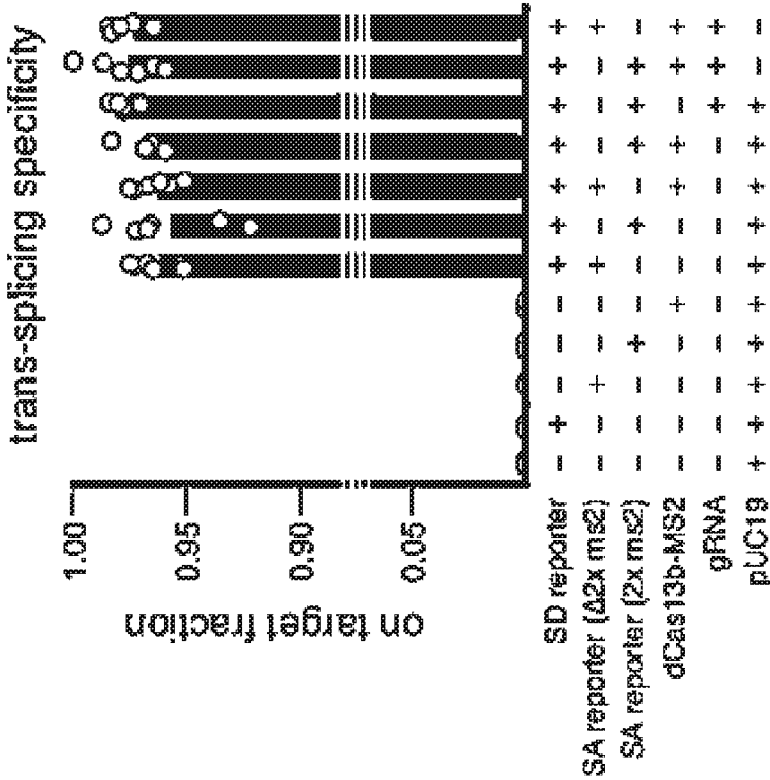


FIG. 3B

5/23

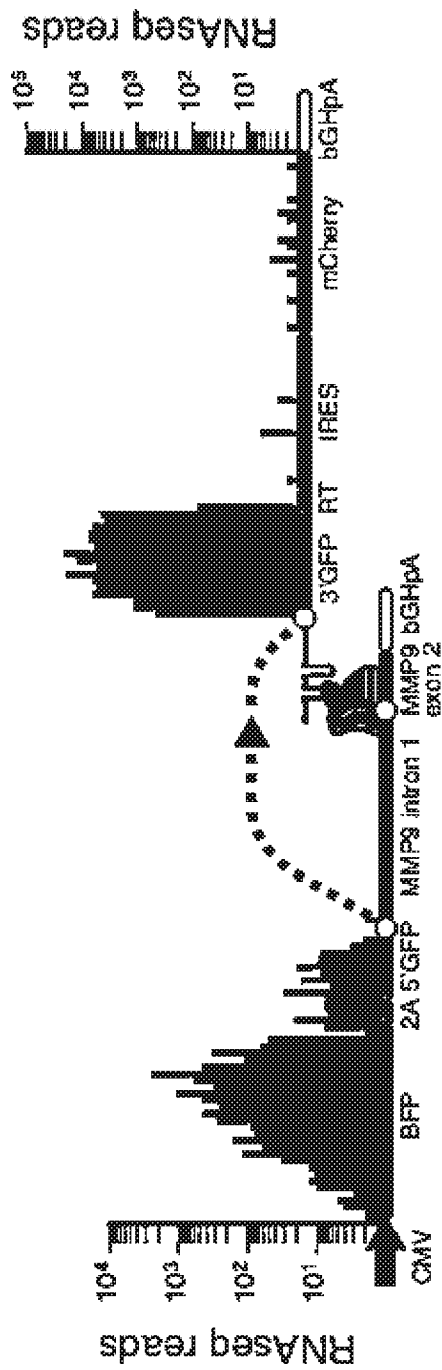


FIG. 4A

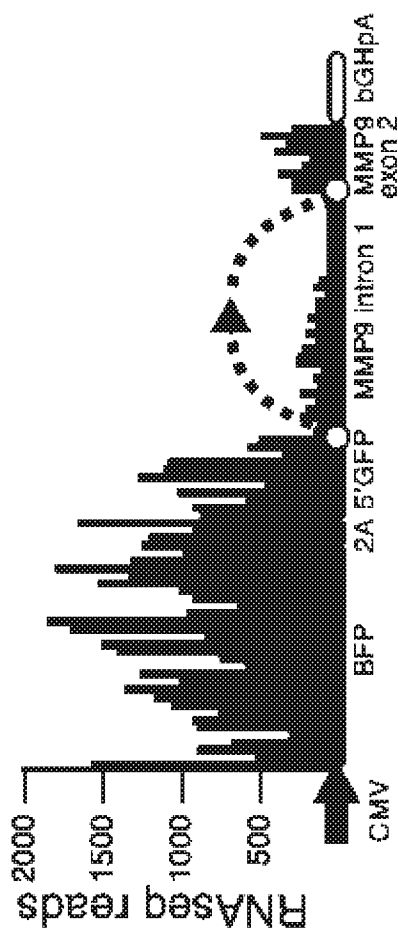


FIG. 4B

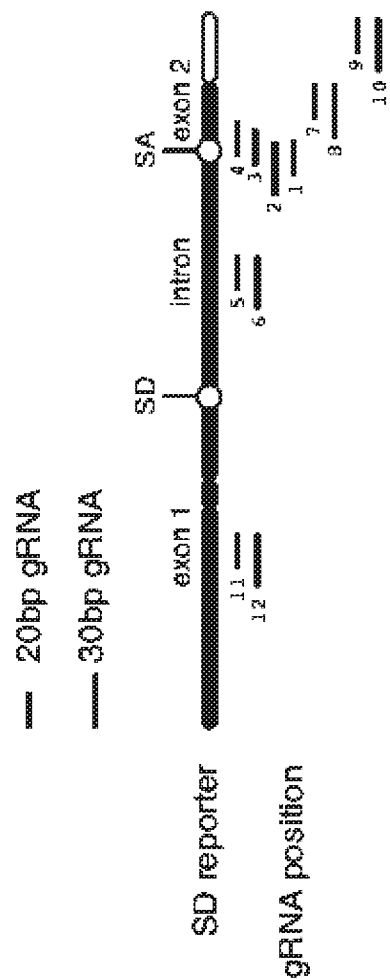


FIG. 5

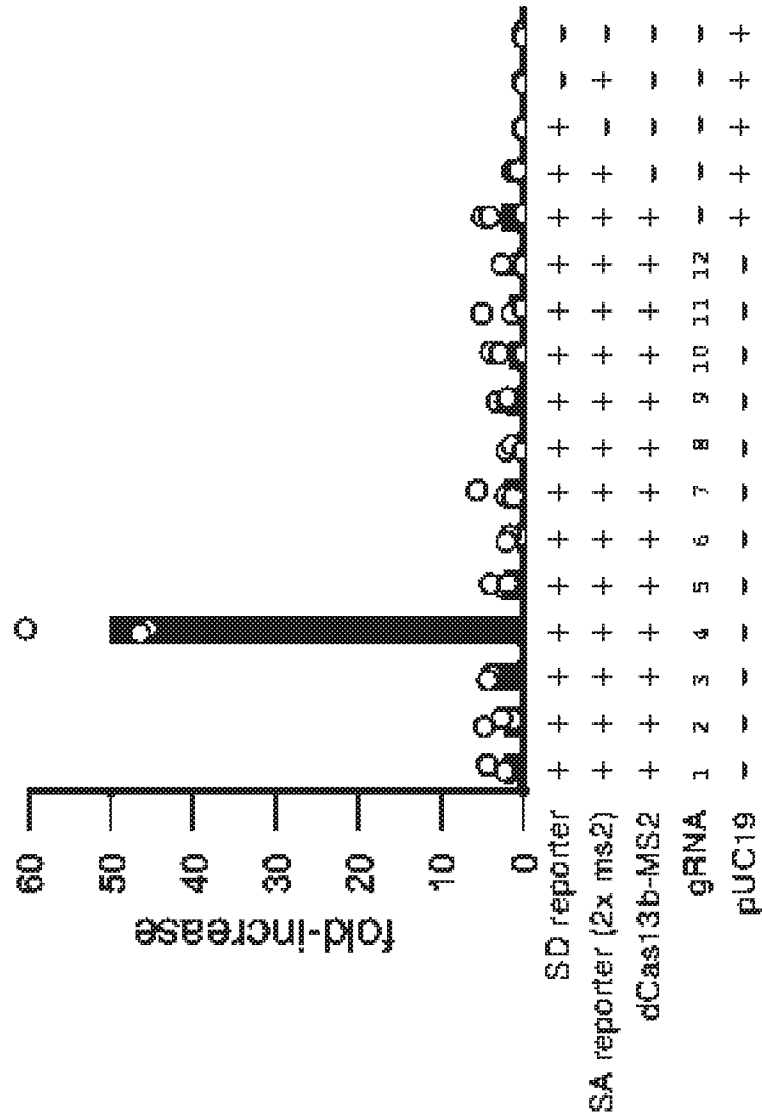


FIG. 6A

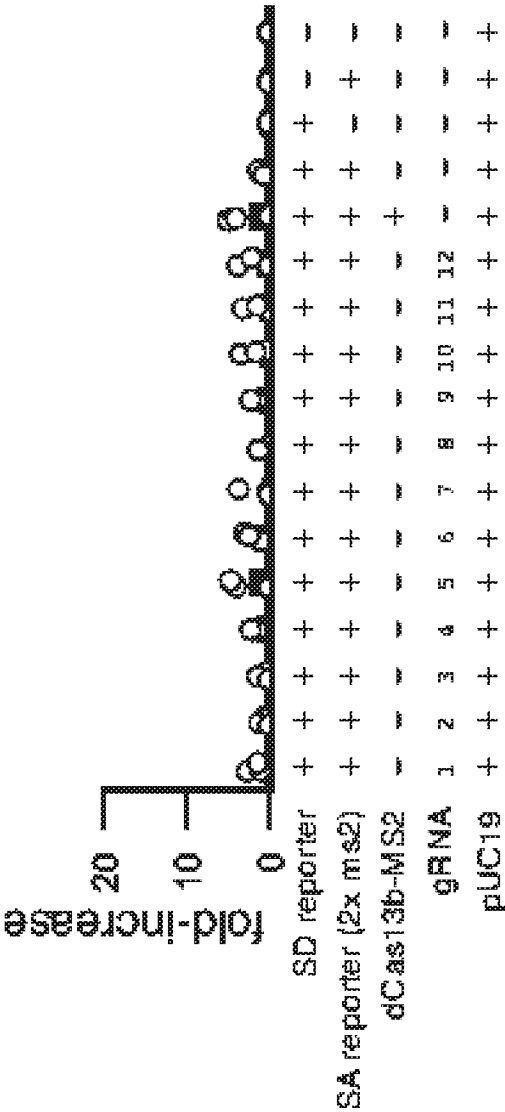


FIG. 6B

9/23

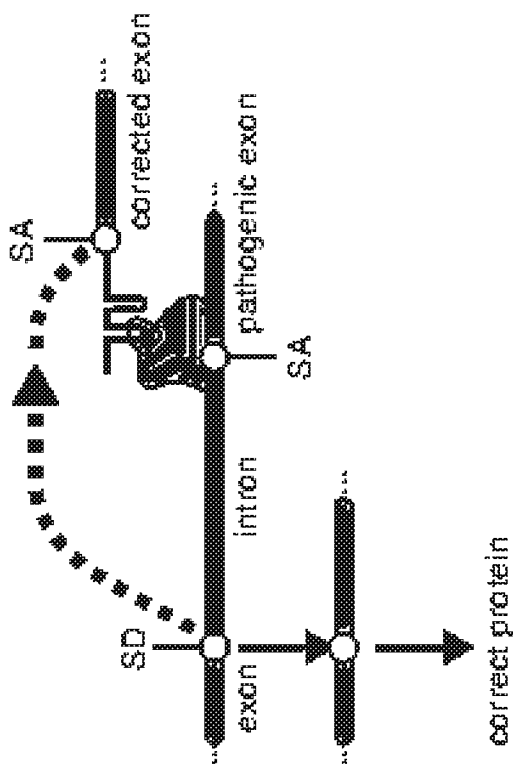


FIG. 7

10/23

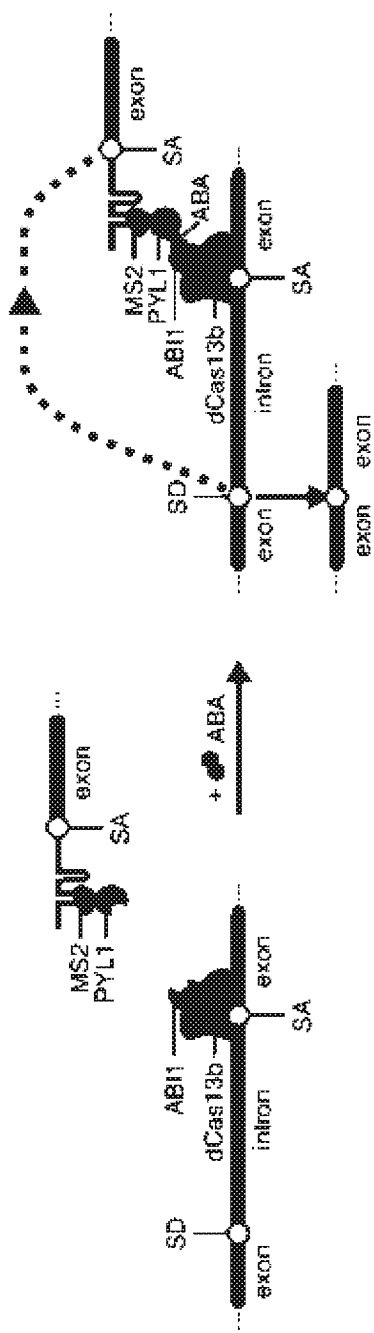


FIG. 8A

11/23

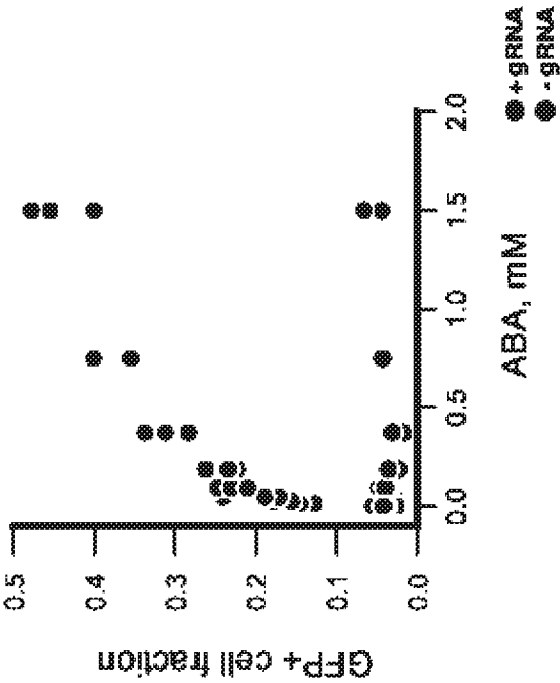


FIG. 8B

12/23

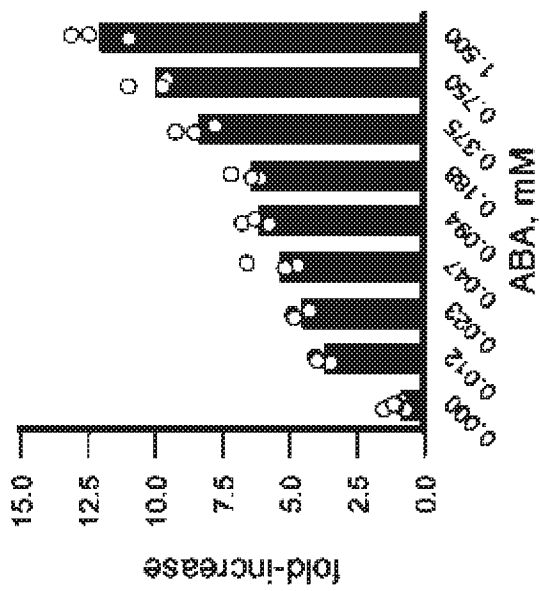


FIG. 8C

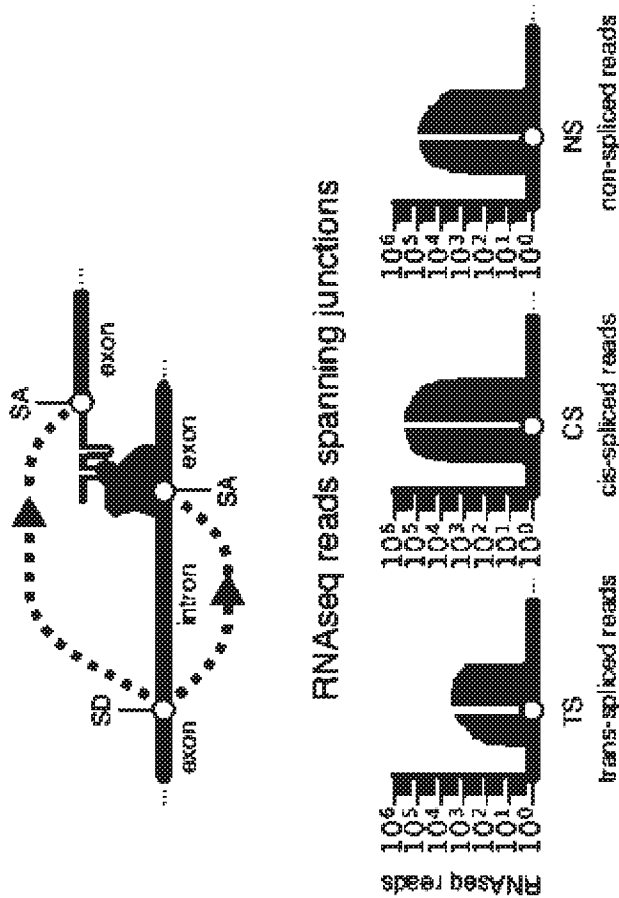


FIG. 9A

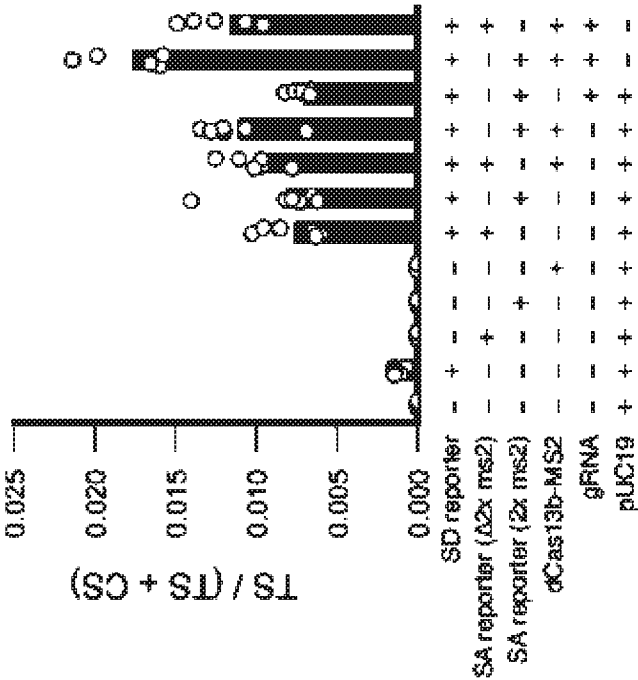


FIG. 9B

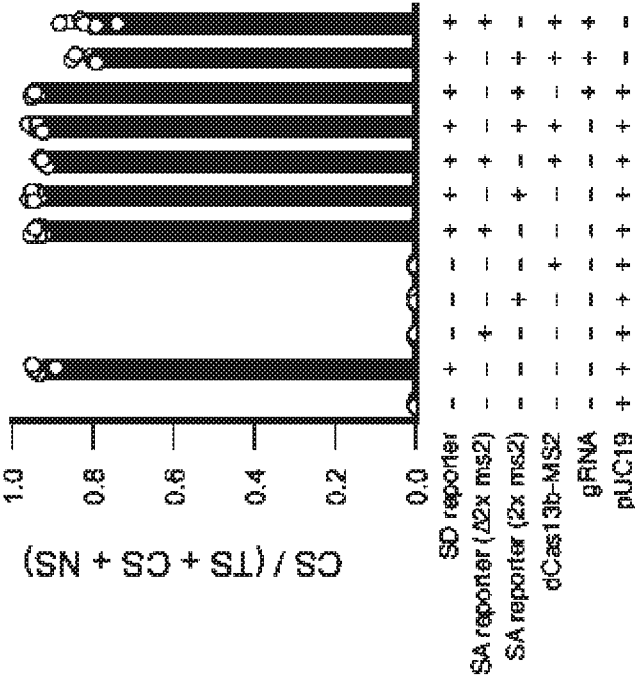


FIG. 9C

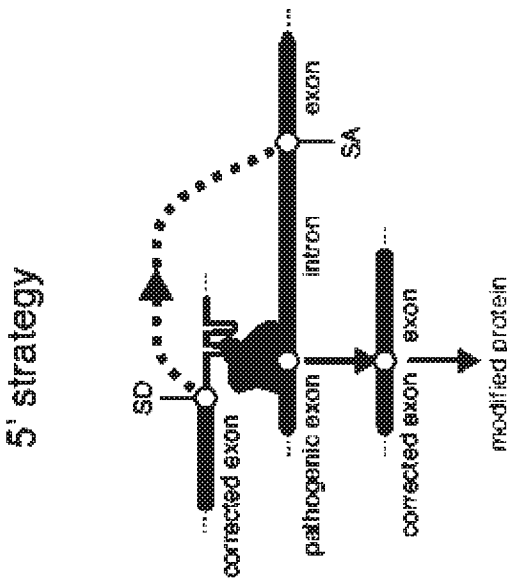


FIG. 10A

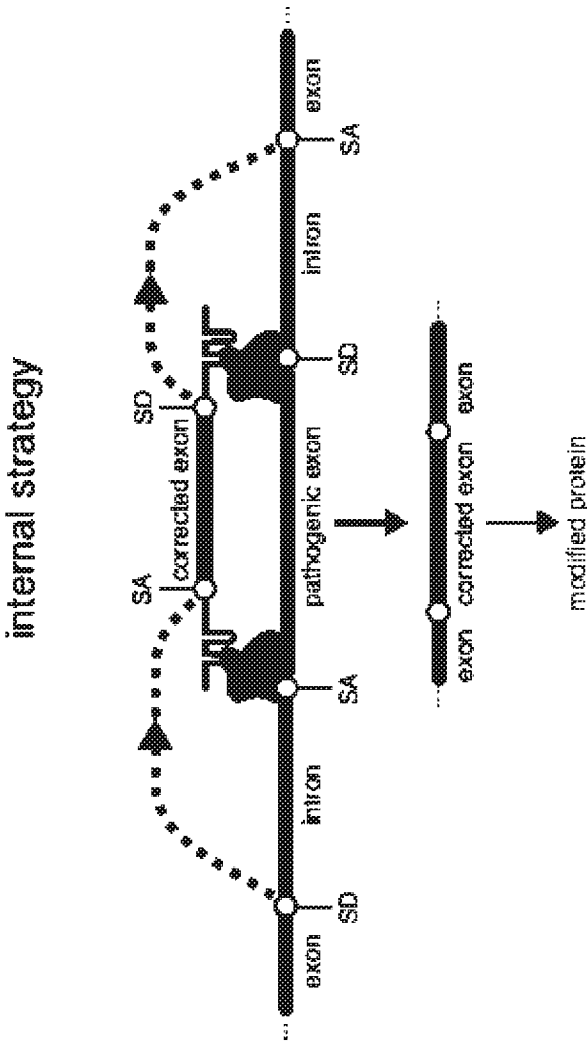


FIG. 10B

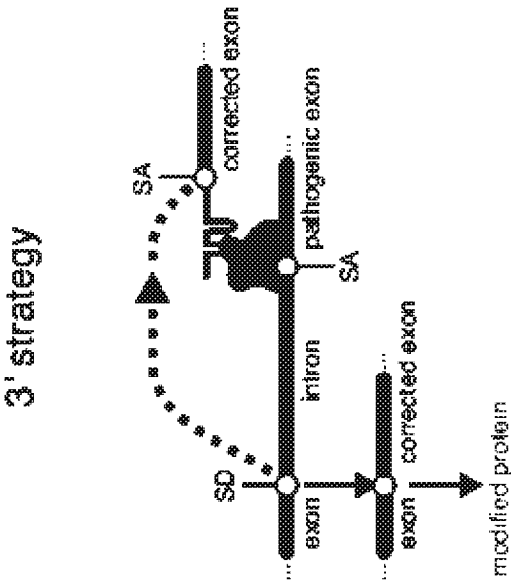


FIG. 10C

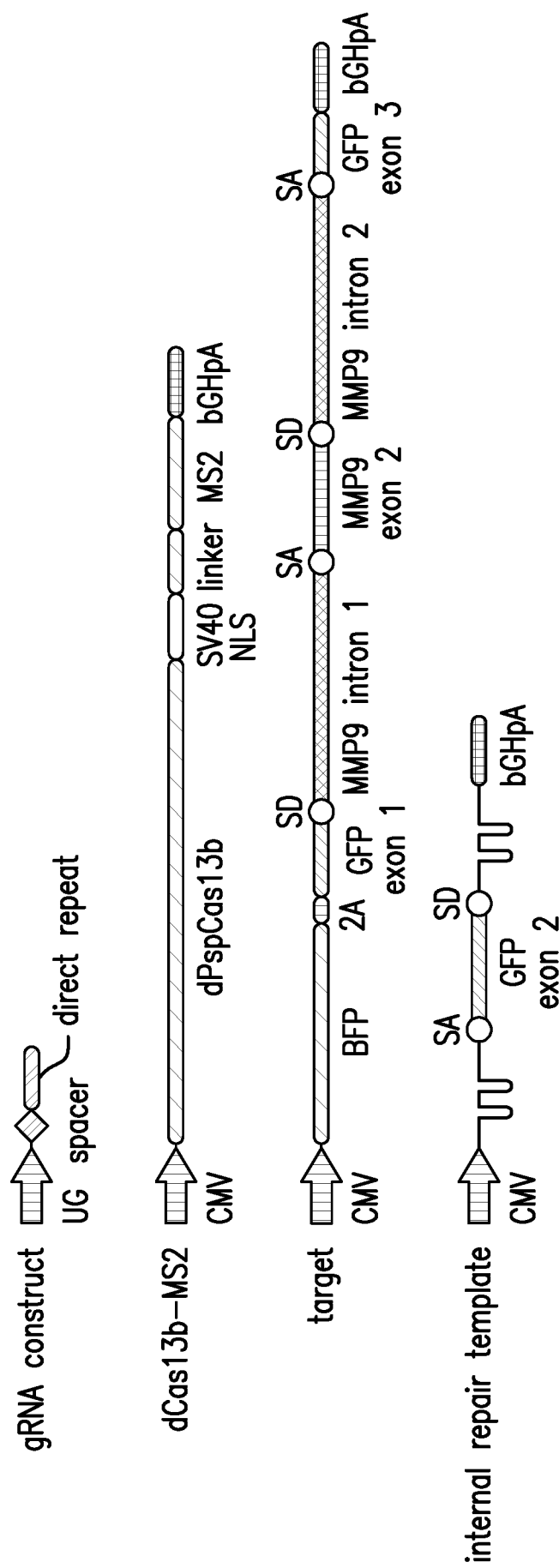


FIG.11A

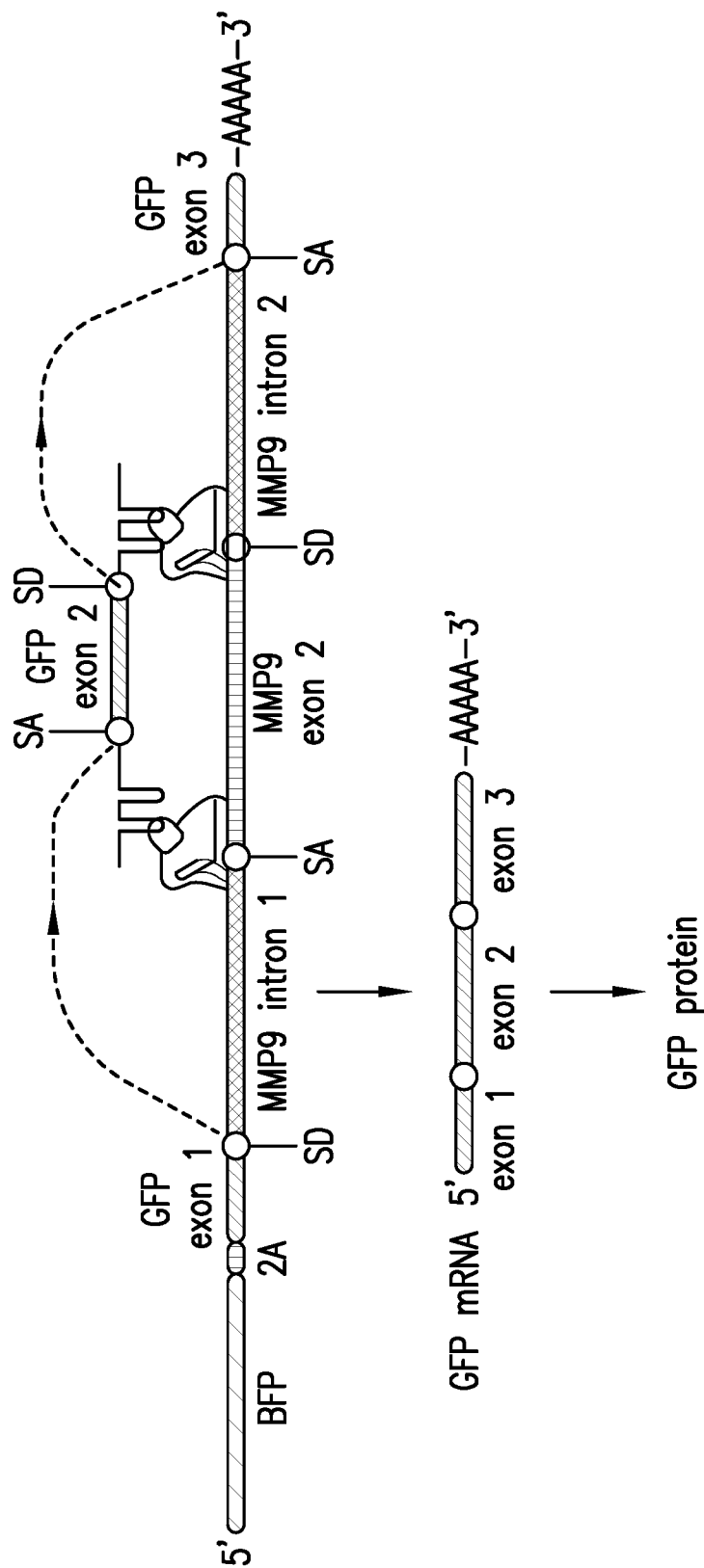


FIG.11B

21/23

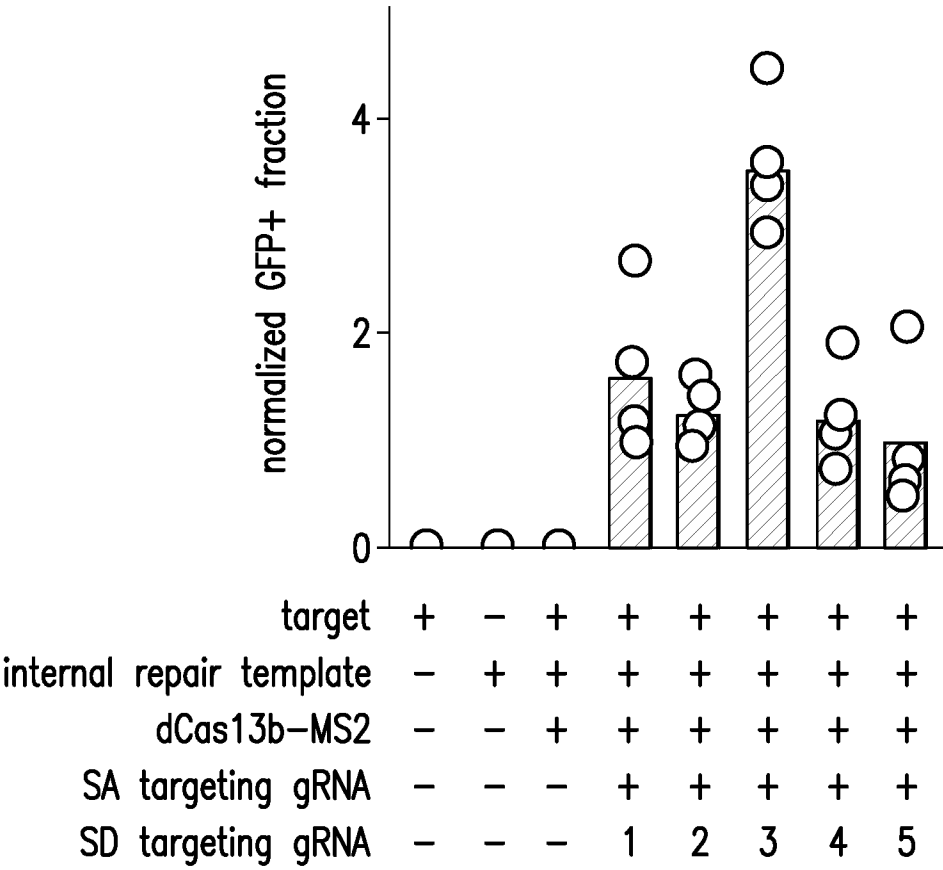


FIG.11C

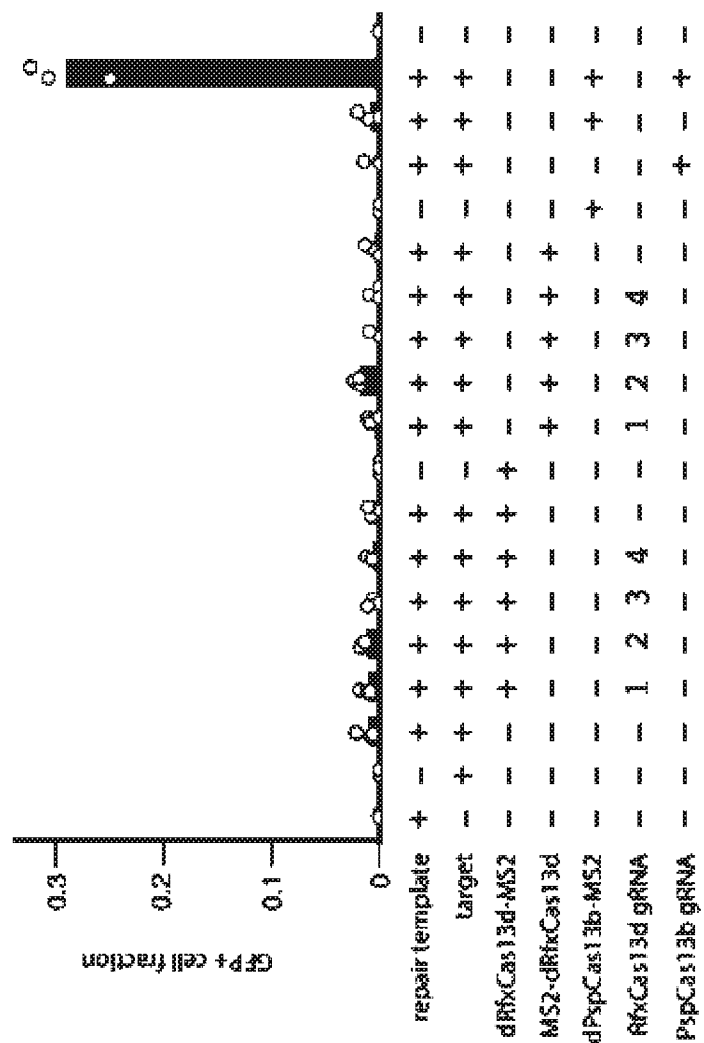


Fig. 2

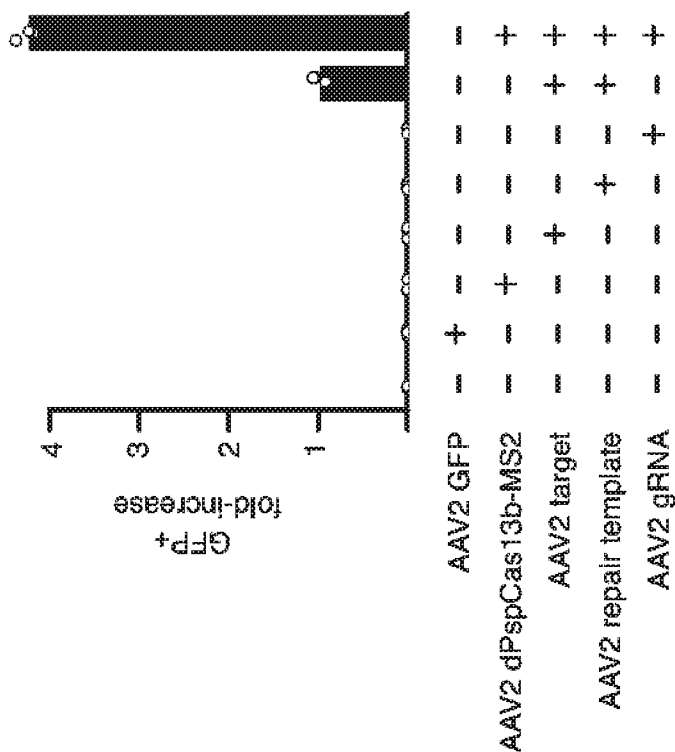


FIG. 13

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<150> 62/888,210

<151> 2019-08-16

<150> 62/985,633

<151> 2020-03-05

<160> 101

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Gln Lys Val Ala Asp Ile Glu Gly Glu Gln Asn Glu Asn Asn Glu Asn
          35           40           45

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Leu Trp Phe His Pro Val Met Ser His Leu Tyr Asn Ala Lys Asn Gly
          50           55           60

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Ser Tyr Phe Pro Phe Leu Lys Ile Met Ala Glu Asn Gln Arg Glu Tyr
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Ser Asn Gly Lys Tyr Lys Gln Asn Arg Val Glu Val Asn Ser Asn Asp
100 105 110

Ile Phe Glu Val Leu Lys Arg Ala Phe Gly Val Leu Lys Met Tyr Arg
115 120 125

Asp Leu Thr Asn Ala Tyr Lys Thr Tyr Glu Glu Lys Leu Asn Asp Gly
130 135 140

Cys Glu Phe Leu Thr Ser Thr Glu Gln Pro Leu Ser Gly Met Ile Asn
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Asn Tyr Tyr Thr Val Ala Leu Arg Asn Met Asn Glu Arg Tyr Gly Tyr
165 170 175

Lys Thr Glu Asp Leu Ala Phe Ile Gln Asp Lys Arg Phe Lys Phe Val
180 185 190

Lys Asp Ala Tyr Gly Lys Lys Lys Ser Gln Val Asn Thr Gly Phe Phe
195 200 205

Leu Ser Leu Gln Asp Tyr Asn Gly Asp Thr Gln Lys Lys Leu His Leu
210 215 220

Ser Gly Val Gly Ile Ala Leu Leu Ile Cys Leu Phe Leu Asp Lys Gln
225 230 235 240

Tyr Ile Asn Ile Phe Leu Ser Arg Leu Pro Ile Phe Ser Ser Tyr Asn
245 250 255

Ala Gln Ser Glu Glu Arg Arg Ile Ile Ile Arg Ser Phe Gly Ile Asn
260 265 270

Ser Ile Lys Leu Pro Lys Asp Arg Ile His Ser Glu Lys Ser Asn Lys
275 280 285

Ser Val Ala Met Asp Met Leu Asn Glu Val Lys Arg Cys Pro Asp Glu
290 295 300

Leu Phe Thr Thr Leu Ser Ala Glu Lys Gln Ser Arg Phe Arg Ile Ile
305 310 315 320

Ser Asp Asp His Asn Glu Val Leu Met Lys Arg Ser Ser Asp Arg Phe
325 330 335

Val Pro Leu Leu Leu Gln Tyr Ile Asp Tyr Gly Lys Leu Phe Asp His
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Ile Arg Phe His Val Asn Met Gly Lys Leu Arg Tyr Leu Leu Lys Ala
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Asp Lys Thr Cys Ile Asp Gly Gln Thr Arg Val Arg Val Ile Glu Gln
370 375 380

Pro Leu Asn Gly Phe Gly Arg Leu Glu Glu Ala Glu Thr Met Arg Lys
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Gln Glu Asn Gly Thr Phe Gly Asn Ser Gly Ile Arg Ile Arg Asp Phe
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Glu Asn Met Lys Arg Asp Asp Ala Asn Pro Ala Asn Tyr Pro Tyr Ile
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Phe Ile Asn Asp Lys Glu Asp Ser Ala Pro Leu Leu Pro Val Ile Glu
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Asp Asp Arg Tyr Val Val Lys Thr Ile Pro Ser Cys Arg Met Ser Thr
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Leu Glu Ile Pro Ala Met Ala Phe His Met Phe Leu Phe Gly Ser Lys
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Lys Thr Glu Lys Leu Ile Val Asp Val His Asn Arg Tyr Lys Arg Leu
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Phe Gly Ile Ala Glu Ser Asp Leu Pro Gln Lys Ile Leu Asp Leu Ile
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Ser Gly Asn Ala His Gly Lys Asp Val Asp Ala Phe Ile Arg Leu Thr
545 550 555 560

Val Asp Asp Met Leu Thr Asp Thr Glu Arg Arg Ile Lys Arg Phe Lys
565 570 575

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580 585 590

Gly Phe Lys Gln Ile Ser Thr Gly Lys Leu Ala Asp Phe Leu Ala Lys
595 600 605

Asp Ile Val Leu Phe Gln Pro Ser Val Asn Asp Gly Glu Asn Lys Ile
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Ser Gly Asp Asp Tyr Glu Ala Lys Gln Gln Phe Lys Leu Met Phe Glu
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660 665 670

Tyr Lys Val Phe Ala Arg Ser Ile Pro Ala Asn Ala Val Glu Phe Tyr
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Glu Arg Tyr Leu Ile Glu Arg Lys Phe Tyr Leu Thr Gly Leu Ser Asn
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Glu Ile Lys Lys Gly Asn Arg Val Asp Val Pro Phe Ile Arg Arg Asp
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Gln Asn Lys Trp Lys Thr Pro Ala Met Lys Thr Leu Gly Arg Ile Tyr
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Lys Val Ile Arg Arg Tyr Arg Val Gln Asp Ala Leu Leu Phe Leu Leu
885 890 895

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915 920 925

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35 40 45

Leu Trp Phe His Pro Val Met Ser His Leu Tyr Asn Ala Lys Asn Gly
50 55 60

Tyr Asp Lys Gln Pro Glu Lys Thr Met Phe Ile Ile Glu Arg Leu Gln
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Ser Tyr Phe Pro Phe Leu Lys Ile Met Ala Glu Asn Gln Arg Glu Tyr
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Ser Asn Gly Lys Tyr Lys Gln Asn Arg Val Glu Val Asn Ser Asn Asp
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Ile Phe Glu Val Leu Lys Arg Ala Phe Gly Val Leu Lys Met Tyr Arg
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Asp Leu Thr Asn Ala Tyr Lys Thr Tyr Glu Glu Lys Leu Asn Asp Gly
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Cys Glu Phe Leu Thr Ser Thr Glu Gln Pro Leu Ser Gly Met Ile Asn
145 150 155 160

Asn Tyr Tyr Thr Val Ala Leu Arg Asn Met Asn Glu Arg Tyr Gly Tyr
165 170 175

Lys Thr Glu Asp Leu Ala Phe Ile Gln Asp Lys Arg Phe Lys Phe Val
180 185 190

Lys Asp Ala Tyr Gly Lys Lys Lys Ser Gln Val Asn Thr Gly Phe Phe
195 200 205

Leu Ser Leu Gln Asp Tyr Asn Gly Asp Thr Gln Lys Lys Leu His Leu
210 215 220

Ser Gly Val Gly Ile Ala Leu Leu Ile Cys Leu Phe Leu Asp Lys Gln
225 230 235 240

Tyr Ile Asn Ile Phe Leu Ser Arg Leu Pro Ile Phe Ser Ser Tyr Asn
245 250 255

Ala Gln Ser Glu Glu Arg Arg Ile Ile Ile Arg Ser Phe Gly Ile Asn
260 265 270

Ser Ile Lys Leu Pro Lys Asp Arg Ile His Ser Glu Lys Ser Asn Lys
275 280 285

Ser Val Ala Met Asp Met Leu Asn Glu Val Lys Arg Cys Pro Asp Glu
290 295 300

Leu Phe Thr Thr Leu Ser Ala Glu Lys Gln Ser Arg Phe Arg Ile Ile
305 310 315 320

Ser Asp Asp His Asn Glu Val Leu Met Lys Arg Ser Ser Asp Arg Phe
325 330 335

Val Pro Leu Leu Leu Gln Tyr Ile Asp Tyr Gly Lys Leu Phe Asp His
340 345 350

Ile Arg Phe His Val Asn Met Gly Lys Leu Arg Tyr Leu Leu Lys Ala
355 360 365

Asp Lys Thr Cys Ile Asp Gly Gln Thr Arg Val Arg Val Ile Glu Gln
370 375 380

Pro Leu Asn Gly Phe Gly Arg Leu Glu Glu Ala Glu Thr Met Arg Lys
385 390 395 400

Gln Glu Asn Gly Thr Phe Gly Asn Ser Gly Ile Arg Ile Arg Asp Phe
405 410 415

Glu Asn Met Lys Arg Asp Asp Ala Asn Pro Ala Asn Tyr Pro Tyr Ile
420 425 430

Val Asp Thr Tyr Thr His Tyr Ile Leu Glu Asn Asn Lys Val Glu Met
435 440 445

Phe Ile Asn Asp Lys Glu Asp Ser Ala Pro Leu Leu Pro Val Ile Glu
450 455 460

Asp Asp Arg Tyr Val Val Lys Thr Ile Pro Ser Cys Arg Met Ser Thr
465 470 475 480

Leu Glu Ile Pro Ala Met Ala Phe His Met Phe Leu Phe Gly Ser Lys
485 490 495

Lys Thr Glu Lys Leu Ile Val Asp Val His Asn Arg Tyr Lys Arg Leu
500 505 510

Phe Gln Ala Met Gln Lys Glu Glu Val Thr Ala Glu Asn Ile Ala Ser
515 520 525

Phe Gly Ile Ala Glu Ser Asp Leu Pro Gln Lys Ile Leu Asp Leu Ile
530 535 540

Ser Gly Asn Ala His Gly Lys Asp Val Asp Ala Phe Ile Arg Leu Thr
545 550 555 560

Val Asp Asp Met Leu Thr Asp Thr Glu Arg Arg Ile Lys Arg Phe Lys
565 570 575

Asp Asp Arg Lys Ser Ile Arg Ser Ala Asp Asn Lys Met Gly Lys Arg
580 585 590

Gly Phe Lys Gln Ile Ser Thr Gly Lys Leu Ala Asp Phe Leu Ala Lys
595 600 605

Asp Ile Val Leu Phe Gln Pro Ser Val Asn Asp Gly Glu Asn Lys Ile
610 615 620

Thr Gly Leu Asn Tyr Arg Ile Met Gln Ser Ala Ile Ala Val Tyr Asp
625 630 635 640

Ser Gly Asp Asp Tyr Glu Ala Lys Gln Gln Phe Lys Leu Met Phe Glu
645 650 655

Lys Ala Arg Leu Ile Gly Lys Gly Thr Thr Glu Pro His Pro Phe Leu
660 665 670

Tyr Lys Val Phe Ala Arg Ser Ile Pro Ala Asn Ala Val Glu Phe Tyr
675 680 685

Glu Arg Tyr Leu Ile Glu Arg Lys Phe Tyr Leu Thr Gly Leu Ser Asn
690 695 700

Glu Ile Lys Lys Gly Asn Arg Val Asp Val Pro Phe Ile Arg Arg Asp
705 710 715 720

Gln Asn Lys Trp Lys Thr Pro Ala Met Lys Thr Leu Gly Arg Ile Tyr
725 730 735

Ser Glu Asp Leu Pro Val Glu Leu Pro Arg Gln Met Phe Asp Asn Glu
740 745 750

Ile Lys Ser His Leu Lys Ser Leu Pro Gln Met Glu Gly Ile Asp Phe
755 760 765

Asn Asn Ala Asn Val Thr Tyr Leu Ile Ala Glu Tyr Met Lys Arg Val
770 775 780

Leu Asp Asp Asp Phe Gln Thr Phe Tyr Gln Trp Asn Arg Asn Tyr Arg
785 790 795 800

Tyr Met Asp Met Leu Lys Gly Glu Tyr Asp Arg Lys Gly Ser Leu Gln
805 810 815

His Cys Phe Thr Ser Val Glu Glu Arg Glu Gly Leu Trp Lys Glu Arg
820 825 830

Ala Ser Arg Thr Glu Arg Tyr Arg Lys Gln Ala Ser Asn Lys Ile Arg
835 840 845

Ser Asn Arg Gln Met Arg Asn Ala Ser Ser Glu Glu Ile Glu Thr Ile
850 855 860

Leu Asp Lys Arg Leu Ser Asn Ser Arg Asn Glu Tyr Gln Lys Ser Glu
865 870 875 880

Lys Val Ile Arg Arg Tyr Arg Val Gln Asp Ala Leu Leu Phe Leu Leu
885 890 895

Ala Lys Lys Thr Leu Thr Glu Leu Ala Asp Phe Asp Gly Glu Arg Phe
900 905 910

Lys Leu Lys Glu Ile Met Pro Asp Ala Glu Lys Gly Ile Leu Ser Glu
915 920 925

Ile Met Pro Met Ser Phe Thr Phe Glu Lys Gly Gly Lys Lys Tyr Thr
930 935 940

Ile Thr Ser Glu Gly Met Lys Leu Lys Asn Tyr Gly Asp Phe Phe Val
945 950 955 960

Leu Ala Ser Asp Lys Arg Ile Gly Asn Leu Leu Glu Leu Val Gly Ser
965 970 975

Asp Ile Val Ser Lys Glu Asp Ile Met Glu Glu Phe Asn Lys Tyr Asp
980 985 990

Gln Cys Arg Pro Glu Ile Ser Ser Ile Val Phe Asn Leu Glu Lys Trp
995 1000 1005

Ala Phe Asp Thr Tyr Pro Glu Leu Ser Ala Arg Val Asp Arg Glu
1010 1015 1020

Glu Lys Val Asp Phe Lys Ser Ile Leu Lys Ile Leu Leu Asn Asn
1025 1030 1035

Lys Asn Ile Asn Lys Glu Gln Ser Asp Ile Leu Arg Lys Ile Arg
1040 1045 1050

Asn Ala Phe Asp Ala Asn Asn Tyr Pro Asp Lys Gly Val Val Glu
1055 1060 1065

Ile Lys Ala Leu Pro Glu Ile Ala Met Ser Ile Lys Lys Ala Phe
1070 1075 1080

Gly Glu Tyr Ala Ile Met Lys Gly Ser Leu Gln Pro Lys Lys Lys
1085 1090 1095

Arg Lys Val Gly Gly Ser Gly Gly Gly Gly Ser Met Ala Ser Asn
1100 1105 1110

Phe Thr Gln Phe Val Leu Val Asp Asn Gly Gly Thr Gly Asp Val
1115 1120 1125

Thr Val Ala Pro Ser Asn Phe Ala Asn Gly Val Ala Glu Trp Ile
1130 1135 1140

Ser Ser Asn Ser Arg Ser Gln Ala Tyr Lys Val Thr Cys Ser Val
1145 1150 1155

Arg Gln Ser Ser Ala Gln Lys Arg Lys Tyr Thr Ile Lys Val Glu
1160 1165 1170

Val Pro Lys Val Ala Thr Gln Thr Val Gly Gly Val Glu Leu Pro
 1175 1180 1185

Val Ala Ala Trp Arg Ser Tyr Leu Asn Met Glu Leu Thr Ile Pro
 1190 1195 1200

Ile Phe Ala Thr Asn Ser Asp Cys Glu Leu Ile Val Lys Ala Met
 1205 1210 1215

Gln Gly Leu Leu Lys Asp Gly Asn Pro Ile Pro Ser Ala Ile Ala
 1220 1225 1230

Ala Asn Ser Gly Ile Tyr
 1235

<210> 5
 <211> 390
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> MS2 coat protein nucleic acid sequence

<400> 5
 atggcctcaa actttactca gttcgtgctc gtggacaatg gtgggacagg ggatgtgaca 60
 gtggctcctt ctaatttcgc taatgggggtg gcagagtgga tcagctccaa ctcacggagc 120
 caggcctaca aggtgacatg cagcgtcagg cagtctagtg cccagaagag aaagtatacc 180
 atcaaggtgg aggtcccaa agtggctacc cagacagtgg gcggagtcga actgcctgtc 240
 gccgcttgga ggtcctacct gaacatggag ctactatcc caattttcgc taccaattct 300
 gactgtgaac tcatcgtgaa ggcaatgcag gggctcctca aagacggtaa tcctatccct 360
 tccgccatcg ccgctaactc aggtatctac 390

<210> 6
 <211> 130
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MS2 coat protein amino acid sequence

<400> 6

Met Ala Ser Asn Phe Thr Gln Phe Val Leu Val Asp Asn Gly Gly Thr
1 5 10 15

Gly Asp Val Thr Val Ala Pro Ser Asn Phe Ala Asn Gly Val Ala Glu
20 25 30

Trp Ile Ser Ser Asn Ser Arg Ser Gln Ala Tyr Lys Val Thr Cys Ser
35 40 45

Val Arg Gln Ser Ser Ala Gln Lys Arg Lys Tyr Thr Ile Lys Val Glu
50 55 60

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

Ala Ala Trp Arg Ser Tyr Leu Asn Met Glu Leu Thr Ile Pro Ile Phe
85 90 95

Ala Thr Asn Ser Asp Cys Glu Leu Ile Val Lys Ala Met Gln Gly Leu
100 105 110

Leu Lys Asp Gly Asn Pro Ile Pro Ser Ala Ile Ala Ala Asn Ser Gly
115 120 125

Ile Tyr
130

<210> 7
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> LambdaN amino acid sequence

<400> 7

Met Asn Ala Arg Thr Arg Arg Arg Glu Arg Arg Ala Glu Lys Gln Ala
1 5 10 15

Gln Trp Lys Ala Ala Asn
20

<210> 8
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> QBeta coat protein amino acid sequeunce

<400> 8

Met Ala Lys Leu Glu Thr Val Thr Leu Gly Asn Ile Gly Lys Asp Gly
1 5 10 15

Lys Gln Thr Leu Val Leu Asn Pro Arg Gly Val Asn Pro Thr Asn Gly
20 25 30

Val Ala Ser Leu Ser Gln Ala Gly Ala Val Arg Ala Leu Glu Lys Arg
35 40 45

Val Thr Val Ser Val Ser Gln Pro Ser Arg Asn Arg Lys Asn Tyr Lys
50 55 60

Val Gln Val Lys Ile Gln Asn Pro Thr Ala Gly Thr Ala Asn Gly Ser
65 70 75 80

Gly Asp Pro Ser Val Thr Arg Gln Ala Tyr Ala Asp Val Thr Phe Ser
85 90 95

Phe Thr Gln Tyr Ser Thr Asp Glu Glu Arg Ala Phe Val Arg Thr Glu
100 105 110

Leu Ala Ala Leu Leu Ala Ser Pro Leu Leu Ile Asp Ala Ile Asp Gln
115 120 125

Leu Arg Pro Ala Tyr
130

<210> 9
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> PP7 coat protein amino acid sequence

<400> 9

Met Ala Ser Lys Thr Ile Val Leu Ser Val Gly Glu Ala Thr Arg Thr
1 5 10 15

Leu Thr Glu Ile Gln Ser Thr Ala Asp Arg Gln Ile Phe Glu Glu Lys
20 25 30

Val Gly Pro Leu Val Gly Arg Leu Arg Leu Thr Ala Ser Leu Arg Gln
35 40 45

Asn Gly Ala Lys Thr Ala Tyr Arg Val Asn Leu Lys Leu Asp Gln Ala
50 55 60

Asp Val Val Asp Ser Gly Leu Pro Lys Val Arg Tyr Thr Gln Val Trp
65 70 75 80

Ser His Asp Val Thr Ile Val Ala Asn Ser Thr Glu Ala Ser Arg Lys
85 90 95

Ser Leu Tyr Asp Leu Thr Lys Ser Leu Val Ala Thr Ser Gln Val Glu
100 105 110

Asp Leu Val Val Asn Leu Val Pro Leu Gly Arg
115 120

<210> 10

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> PspCas13b direct repeat

<400> 10

gttgtggaag gtccagtttt gaggggctat tacaac

36

<210> 11

<211> 56

<212> DNA

<213> Artificial Sequence

<220>

<223> PspCas13 gRNA

<220>
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 <222> (1)..(20)
 <223> n is a, c, g, or t

<400> 11
 nnnnnnnnnn nnnnnnnnnn gttgtggaag gtccagtttt gaggggctat tacaac 56

<210> 12
 <211> 56
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PspCas13b gRNA

<400> 12
 tagcgggtaca ggtattcctg gttgtggaag gtccagtttt gaggggctat tacaac 56

<210> 13
 <211> 19
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> MS2 hairpin

<400> 13
 acatgaggat cacccatgt 19

<210> 14
 <211> 17
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> boxB hairpin

<400> 14
 ggccctgaaa aagggcc 17

<210> 15
 <211> 20
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> QBeta hairpin

<400> 15
atgcatgtct aagacagcat 20

<210> 16
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> PP7 hairpin

<400> 16
taaggagttt atatggaaac cctta 25

<210> 17
<211> 4170
<212> DNA
<213> Artificial Sequence

<220>
<223> LshCas13a nucleic acid sequence

<400> 17
atggggaacc tggtcggaca caagcgggtg tacgaggtgc gagataagaa agacttcaag 60
atcaagcgaa aggtgaaagt caagcgggaat tatgacggga acaagtacat tctgaacatc 120
aacgaaaaca acaacaaaga gaagatcgac aacaacaagt tcatcagaaa gtacatcaac 180
tacaagaaaa acgataatat tctgaaggag ttcactagga aatttcatgc aggaaatattc 240
ctgttcaaac tgaagggcaa agaagggatc attagaattg agaataacga cgacttcctg 300
gagacagagg aagtgggtgct gtatatcgag gcctacggca agagcgagaa gctgaaagca 360
ctgggggatca caaagaaaaa gatcattgac gaggccatca ggcagggcat tactaaggac 420
gataaaaaga tcgagatcaa gcgacaggag aacgaggaag agatcgaaat tgacatccgg 480
gatgagtaca ctaataagac cctgaacgac tgctccatca ttctgcgcat cattgaaaac 540
gatgaactgg agacaaagaa gagcatctac gagatcttca agaacatcaa tatgagcctg 600
tataagatca tcgagaagat catcgaaaac gagacagaaa aggtgtttga aaatagatac 660
tacgaagagc acctgaggga gaagctgctg aaagacgata agattgacgt gacacctgacc 720
aacttcatgg aaatccggga gaagatcaag tctaattctgg agatcctggg cttcgtgaag 780
ttttacctga acgtcggcgg ggacaaaaag aaaagtaaaa ataagaaaat gctgggtggaa 840
aagattctga acatcaatgt ggatctgacc gtcgaggaca ttgccgattt cgtgatcaag 900

gagctggaat tttggaacat cacaaagcgc attgagaaag tgaagaaagt caataacgag	960
ttcctggaga agcggagaaa tcggacatac atcaagtcct atgtgctgct ggacaagcac	1020
gaaaagttta aaatcgagag agaaaacaag aaggataaga tcgtgaagtt ctttgtcgag	1080
aacattaaga acaactctat caaggaaaag attgagaaga tcctggctga gttcaagatc	1140
gacgagctga ttaagaaact ggagaaggaa ctgaagaaag ggaactgtga taccgagatc	1200
ttcggaatct ttaagaagca ttacaaggtg aacttcgaca gcaagaaatt ttccaagaaa	1260
tctgatgaag agaaggagct gtataagatc atctacagat acctgaaggg cagaattgaa	1320
aaaatcctgg tgaacgagca gaaggtcaga ctgaagaaaa tggagaagat cgagatcgaa	1380
aagattctga atgaaagtat cctgtcagag aaaattctga agagagtga acagtataca	1440
ctggagcaca ttatgtacct ggggaagctg aggcataacg acatcgatat gaccacagtg	1500
aatactgacg atttcagccg cctgcacgcc aaggaagagc tggacctgga actgatcacc	1560
ttctttgcca gcacaaatat ggagctgaac aagatctttt cccgagaaaa catcaacaac	1620
gacgagaaca tcgatttctt tggaggcgac cgggagaaga actatgtgct ggataagaaa	1680
atcctgaata gtaagatcaa gatcatccgc gacctggatt tcatcgataa caagaacaac	1740
atcacaaaca acttcattcg aaagtttaca aagatcggca ctaatgaaag gaaccgcac	1800
ctgcatgcca tttccaaaga gagggacctg caggggactc aggacgatta caacaaagt	1860
atcaacatca ttcagaatct gaagatctcc gatgaagagg tgagcaaagc tctgaacctg	1920
gacgtggtct ttaaggacaa gaaaaacatc atcacaaaga tcaatgacat caagatctct	1980
gaagagaaca acaacgatat caagtatctg cccagcttca gcaaagtgt gcccgaatc	2040
ctgaacctgt accgcaaca tcccaagaat gagccttttg acacaatcga gactgaaaaa	2100
attgtgctga acgctctgat ctacgtcaat aaggagctgt ataagaaact gatcctggag	2160
gacgatctgg aagagaacga gtccaagaat atcttcctgc aggaactgaa gaaaaccctg	2220
ggcaacattg acgaaatcga tgagaacatc atcgagaact actacaagaa cgcacagatt	2280
tctgccagta aggggaacaa caaggcaatc aagaaatatc agaagaaagt gatcgagtgc	2340
tacattggat atctgcgcaa aaactacgaa gagctgttcg acttttcaga cttcaagatg	2400
aacatccagg aaatcaagaa acagattaag gacatcaacg ataacaagac ttatgagtgg	2460
atcaccgtga aaaccagcga caaaaccatt gtcacatcaacg acgatttcga gtacatcatt	2520

tctatctttg cactgctgaa cagtaatgcc gtgattaata agatccgaaa cagattcttc	2580
gccaccagcg tgtggctgaa cacctcagaa taccagaata tcattgacat cctggatgag	2640
attatgcagc tgaataccct gcggaacgaa tgcatcacag agaactggaa tctgaacctg	2700
gaagagttca ttcagaagat gaaagagatc gaaaaggatt tcgacgactt caagatccag	2760
actaagaaag aaatcttcaa caactactac gaggacatca agaacaacat tctgaccgag	2820
tttaaagacg atatcaacgg ctgtgatgtg ctggaaaaga aactggagaa gattgtcatc	2880
ttcgacgatg aaaccaagtt cgagatcgac aagaaatcca acatcctgca ggatgaacag	2940
agaaagctgt ctaacatcaa caagaaggac ctgaagaaaa aggtggatca gtatatcaag	3000
gacaaagatc aggagatcaa gtctaaaatc ctgtgcagga tcattttcaa cagtgacttt	3060
ctgaaaaagt acaagaagga aatcgacaat ctgattgagg atatggagtc tgaaaatgag	3120
aacaagttcc aggagatcta ctatcccaag gaacggaaga acgagctgta tatctacaaa	3180
aagaatctgt tcctgaacat cggaaatcct aactttgaca agatctacgg cctgattagc	3240
aacgacatca agatggccga tgctaaattc ctgtttaata tcgatggaaa gaacatcaga	3300
aagaacaaaa tcagtgagat cgacgctatt ctgaagaatc tgaacgataa actgaacggc	3360
tactcaaagg aatacaagga gaagtacatc aaaaagctga aggagaacga cgatttcttt	3420
gcaaagaaca tccagaataa gaactacaaa tccttcgaaa aggactataa ccgcgtgtct	3480
gagtacaaaa agattcgaga tctggctcgag ttcaactatc tgaacaaaat cgagtcctac	3540
ctgattgaca tcaactggaa gctggctatt cagatggcaa gattcgaaag ggatatgcac	3600
tatatcgtga atggactgag ggagctgggc atcattaagc tgtcaggcta taacaccggg	3660
atcagcaggg catacccaaa gcgcaatgga agcgacggct ttacactac cacagcctac	3720
tacaagttct ttgatgaaga gtcctacaag aagttcgaga agatttgcta cgggtttgga	3780
atcgacctga gcgaaaattc cgagatcaac aagcctgaaa atgagagcat tcggaactat	3840
atctcccatt tctacatcgt gagaaatcca tttgccgact acagtattgc tgagcagatc	3900
gatcgggtga gcaacctgct gtcatatagc acacgctaca acaattcaac ttatgccagc	3960
gtgttcgaag tctttaaaaa ggacgtgaat ctggactacg atgagctgaa aaagaaattc	4020
aaactgatcg gcaacaatga tattctggag cgcctgatga agcccaagaa agtgagcgtc	4080
ctggaactgg agtcctacaa cagtgactac attaagaatc tgatcattga actgctgacc	4140

aaaatcgaga atactaacga taccctgtga

4170

<210> 18

<211> 1389

<212> PRT

<213> Artificial Sequence

<220>

<223> LshCas13a amino acid sequence

<400> 18

Met Gly Asn Leu Phe Gly His Lys Arg Trp Tyr Glu Val Arg Asp Lys
1 5 10 15

Lys Asp Phe Lys Ile Lys Arg Lys Val Lys Val Lys Arg Asn Tyr Asp
20 25 30

Gly Asn Lys Tyr Ile Leu Asn Ile Asn Glu Asn Asn Asn Lys Glu Lys
35 40 45

Ile Asp Asn Asn Lys Phe Ile Arg Lys Tyr Ile Asn Tyr Lys Lys Asn
50 55 60

Asp Asn Ile Leu Lys Glu Phe Thr Arg Lys Phe His Ala Gly Asn Ile
65 70 75 80

Leu Phe Lys Leu Lys Gly Lys Glu Gly Ile Ile Arg Ile Glu Asn Asn
85 90 95

Asp Asp Phe Leu Glu Thr Glu Glu Val Val Leu Tyr Ile Glu Ala Tyr
100 105 110

Gly Lys Ser Glu Lys Leu Lys Ala Leu Gly Ile Thr Lys Lys Lys Ile
115 120 125

Ile Asp Glu Ala Ile Arg Gln Gly Ile Thr Lys Asp Asp Lys Lys Ile
130 135 140

Glu Ile Lys Arg Gln Glu Asn Glu Glu Glu Ile Glu Ile Asp Ile Arg
145 150 155 160

Asp Glu Tyr Thr Asn Lys Thr Leu Asn Asp Cys Ser Ile Ile Leu Arg
165 170 175

Ile Ile Glu Asn Asp Glu Leu Glu Thr Lys Lys Ser Ile Tyr Glu Ile
180 185 190

Phe Lys Asn Ile Asn Met Ser Leu Tyr Lys Ile Ile Glu Lys Ile Ile
195 200 205

Glu Asn Glu Thr Glu Lys Val Phe Glu Asn Arg Tyr Tyr Glu Glu His
210 215 220

Leu Arg Glu Lys Leu Leu Lys Asp Asp Lys Ile Asp Val Ile Leu Thr
225 230 235 240

Asn Phe Met Glu Ile Arg Glu Lys Ile Lys Ser Asn Leu Glu Ile Leu
245 250 255

Gly Phe Val Lys Phe Tyr Leu Asn Val Gly Gly Asp Lys Lys Lys Ser
260 265 270

Lys Asn Lys Lys Met Leu Val Glu Lys Ile Leu Asn Ile Asn Val Asp
275 280 285

Leu Thr Val Glu Asp Ile Ala Asp Phe Val Ile Lys Glu Leu Glu Phe
290 295 300

Trp Asn Ile Thr Lys Arg Ile Glu Lys Val Lys Lys Val Asn Asn Glu
305 310 315 320

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

Leu Asp Lys His Glu Lys Phe Lys Ile Glu Arg Glu Asn Lys Lys Asp
340 345 350

Lys Ile Val Lys Phe Phe Val Glu Asn Ile Lys Asn Asn Ser Ile Lys
355 360 365

Glu Lys Ile Glu Lys Ile Leu Ala Glu Phe Lys Ile Asp Glu Leu Ile
370 375 380

Lys Lys Leu Glu Lys Glu Leu Lys Lys Gly Asn Cys Asp Thr Glu Ile
385 390 395 400

Phe Gly Ile Phe Lys Lys His Tyr Lys Val Asn Phe Asp Ser Lys Lys
405 410 415

Phe Ser Lys Lys Ser Asp Glu Glu Lys Glu Leu Tyr Lys Ile Ile Tyr
420 425 430

Arg Tyr Leu Lys Gly Arg Ile Glu Lys Ile Leu Val Asn Glu Gln Lys
435 440 445

Val Arg Leu Lys Lys Met Glu Lys Ile Glu Ile Glu Lys Ile Leu Asn
450 455 460

Glu Ser Ile Leu Ser Glu Lys Ile Leu Lys Arg Val Lys Gln Tyr Thr
465 470 475 480

Leu Glu His Ile Met Tyr Leu Gly Lys Leu Arg His Asn Asp Ile Asp
485 490 495

Met Thr Thr Val Asn Thr Asp Asp Phe Ser Arg Leu His Ala Lys Glu
500 505 510

Glu Leu Asp Leu Glu Leu Ile Thr Phe Phe Ala Ser Thr Asn Met Glu
515 520 525

Leu Asn Lys Ile Phe Ser Arg Glu Asn Ile Asn Asn Asp Glu Asn Ile
530 535 540

Asp Phe Phe Gly Gly Asp Arg Glu Lys Asn Tyr Val Leu Asp Lys Lys
545 550 555 560

Ile Leu Asn Ser Lys Ile Lys Ile Ile Arg Asp Leu Asp Phe Ile Asp
565 570 575

Asn Lys Asn Asn Ile Thr Asn Asn Phe Ile Arg Lys Phe Thr Lys Ile
580 585 590

Gly Thr Asn Glu Arg Asn Arg Ile Leu His Ala Ile Ser Lys Glu Arg
595 600 605

Asp Leu Gln Gly Thr Gln Asp Asp Tyr Asn Lys Val Ile Asn Ile Ile
610 615 620

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

Asp Val Val Phe Lys Asp Lys Lys Asn Ile Ile Thr Lys Ile Asn Asp
645 650 655

Ile Lys Ile Ser Glu Glu Asn Asn Asn Asp Ile Lys Tyr Leu Pro Ser
660 665 670

Phe Ser Lys Val Leu Pro Glu Ile Leu Asn Leu Tyr Arg Asn Asn Pro
675 680 685

Lys Asn Glu Pro Phe Asp Thr Ile Glu Thr Glu Lys Ile Val Leu Asn
690 695 700

Ala Leu Ile Tyr Val Asn Lys Glu Leu Tyr Lys Lys Leu Ile Leu Glu
705 710 715 720

Asp Asp Leu Glu Glu Asn Glu Ser Lys Asn Ile Phe Leu Gln Glu Leu
725 730 735

Lys Lys Thr Leu Gly Asn Ile Asp Glu Ile Asp Glu Asn Ile Ile Glu
740 745 750

Asn Tyr Tyr Lys Asn Ala Gln Ile Ser Ala Ser Lys Gly Asn Asn Lys
755 760 765

Ala Ile Lys Lys Tyr Gln Lys Lys Val Ile Glu Cys Tyr Ile Gly Tyr
770 775 780

Leu Arg Lys Asn Tyr Glu Glu Leu Phe Asp Phe Ser Asp Phe Lys Met
785 790 795 800

Asn Ile Gln Glu Ile Lys Lys Gln Ile Lys Asp Ile Asn Asp Asn Lys
805 810 815

Thr Tyr Glu Trp Ile Thr Val Lys Thr Ser Asp Lys Thr Ile Val Ile
820 825 830

Asn Asp Asp Phe Glu Tyr Ile Ile Ser Ile Phe Ala Leu Leu Asn Ser
835 840 845

Asn Ala Val Ile Asn Lys Ile Arg Asn Arg Phe Phe Ala Thr Ser Val
850 855 860

Trp Leu Asn Thr Ser Glu Tyr Gln Asn Ile Ile Asp Ile Leu Asp Glu
865 870 875 880

Ile Met Gln Leu Asn Thr Leu Arg Asn Glu Cys Ile Thr Glu Asn Trp
885 890 895

Asn Leu Asn Leu Glu Glu Phe Ile Gln Lys Met Lys Glu Ile Glu Lys
900 905 910

Asp Phe Asp Asp Phe Lys Ile Gln Thr Lys Lys Glu Ile Phe Asn Asn
915 920 925

Tyr Tyr Glu Asp Ile Lys Asn Asn Ile Leu Thr Glu Phe Lys Asp Asp
930 935 940

Ile Asn Gly Cys Asp Val Leu Glu Lys Lys Leu Glu Lys Ile Val Ile
945 950 955 960

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

Gln Asp Glu Gln Arg Lys Leu Ser Asn Ile Asn Lys Lys Asp Leu Lys
980 985 990

Lys Lys Val Asp Gln Tyr Ile Lys Asp Lys Asp Gln Glu Ile Lys Ser
995 1000 1005

Lys Ile Leu Cys Arg Ile Ile Phe Asn Ser Asp Phe Leu Lys Lys
1010 1015 1020

Tyr Lys Lys Glu Ile Asp Asn Leu Ile Glu Asp Met Glu Ser Glu
1025 1030 1035

Asn Glu Asn Lys Phe Gln Glu Ile Tyr Tyr Pro Lys Glu Arg Lys
1040 1045 1050

Asn Glu Leu Tyr Ile Tyr Lys Lys Asn Leu Phe Leu Asn Ile Gly
1055 1060 1065

Asn Pro Asn Phe Asp Lys Ile Tyr Gly Leu Ile Ser Asn Asp Ile
1070 1075 1080

Lys Met Ala Asp Ala Lys Phe Leu Phe Asn Ile Asp Gly Lys Asn
1085 1090 1095

Ile Arg Lys Asn Lys Ile Ser Glu Ile Asp Ala Ile Leu Lys Asn
1100 1105 1110

Leu Asn Asp Lys Leu Asn Gly Tyr Ser Lys Glu Tyr Lys Glu Lys
1115 1120 1125

Tyr Ile Lys Lys Leu Lys Glu Asn Asp Asp Phe Phe Ala Lys Asn
1130 1135 1140

Ile Gln Asn Lys Asn Tyr Lys Ser Phe Glu Lys Asp Tyr Asn Arg
1145 1150 1155

Val Ser Glu Tyr Lys Lys Ile Arg Asp Leu Val Glu Phe Asn Tyr
1160 1165 1170

Leu Asn Lys Ile Glu Ser Tyr Leu Ile Asp Ile Asn Trp Lys Leu
1175 1180 1185

Ala Ile Gln Met Ala Arg Phe Glu Arg Asp Met His Tyr Ile Val
1190 1195 1200

Asn Gly Leu Arg Glu Leu Gly Ile Ile Lys Leu Ser Gly Tyr Asn
1205 1210 1215

Thr Gly Ile Ser Arg Ala Tyr Pro Lys Arg Asn Gly Ser Asp Gly
1220 1225 1230

Phe Tyr Thr Thr Thr Ala Tyr Tyr Lys Phe Phe Asp Glu Glu Ser
1235 1240 1245

Tyr Lys Lys Phe Glu Lys Ile Cys Tyr Gly Phe Gly Ile Asp Leu
1250 1255 1260

Ser Glu Asn Ser Glu Ile Asn Lys Pro Glu Asn Glu Ser Ile Arg
1265 1270 1275

Asn Tyr Ile Ser His Phe Tyr Ile Val Arg Asn Pro Phe Ala Asp
1280 1285 1290

Tyr Ser Ile Ala Glu Gln Ile Asp Arg Val Ser Asn Leu Leu Ser
1295 1300 1305

Tyr Ser Thr Arg Tyr Asn Asn Ser Thr Tyr Ala Ser Val Phe Glu
1310 1315 1320

Val Phe Lys Lys Asp Val Asn Leu Asp Tyr Asp Glu Leu Lys Lys
1325 1330 1335

Lys Phe Lys Leu Ile Gly Asn Asn Asp Ile Leu Glu Arg Leu Met
1340 1345 1350

Lys Pro Lys Lys Val Ser Val Leu Glu Leu Glu Ser Tyr Asn Ser
1355 1360 1365

Asp Tyr Ile Lys Asn Leu Ile Ile Glu Leu Leu Thr Lys Ile Glu
1370 1375 1380

Asn Thr Asn Asp Thr Leu
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<210> 19

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> LshCas13a direct repeat

<400> 19
ccacccaat atcgaagggg actaaaac 28

<210> 20
<211> 3456
<212> DNA
<213> Artificial Sequence

<220>
<223> LwaCas13a nucleic acid sequence

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cggctggaca tctacatcaa gaaccccgac aacgcctccg aggaagagaa ccggatcaga 180
agagagaacc tgaagaagtt ctttagcaac aaggtgctgc acctgaagga cagcgtgctg 240
tatctgaaga accggaaaga aaagaacgcc gtgcaggaca agaactatag cgaagaggac 300
atcagcgagt acgacctgaa aaacaagaac agcttctccg tgctgaagaa gatcctgctg 360
aacgaggacg tgaactctga ggaactggaa atctttcgga aggacgtgga agccaagctg 420
aacaagatca acagcctgaa gtacagcttc gaagagaaca aggccaacta ccagaagatc 480
aacgagaaca acgtggaaaa agtgggcggc aagagcaagc ggaacatcat ctacgactac 540
tacagagaga gcgccaagcg caacgactac atcaacaacg tgcaggaagc cttcgacaag 600
ctgtataaga aagaggatat cgagaaactg tttttcctga tcgagaacag caagaagcac 660
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gagaacggta tcaccggccg gatgcggggc aagaccgtga agaacaacaa gggcgaagag 1260

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gaggactaca	aagagtatga	gaaggccatc	ggcaacatcc	agaagtacac	ccacctgaag	2820
aacaaggtgg	aattcaatga	gctgaacctg	ctgcagggcc	tgctgctgaa	gatcctgcac	2880

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 aatgtggaaa agcggagcat ctactccgac aagaaagtga agaaactgaa gcaggaaaaa 3120
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<210> 21
 <211> 1152
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> LwaCas13 amino acid sequence

<400> 21

Met Lys Val Thr Lys Val Asp Gly Ile Ser His Lys Lys Tyr Ile Glu
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Glu Gly Lys Leu Val Lys Ser Thr Ser Glu Glu Asn Arg Thr Ser Glu
 20 25 30

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

Pro Asp Asn Ala Ser Glu Glu Glu Asn Arg Ile Arg Arg Glu Asn Leu
 50 55 60

Lys Lys Phe Phe Ser Asn Lys Val Leu His Leu Lys Asp Ser Val Leu
 65 70 75 80

Tyr Leu Lys Asn Arg Lys Glu Lys Asn Ala Val Gln Asp Lys Asn Tyr
 85 90 95

Ser Glu Glu Asp Ile Ser Glu Tyr Asp Leu Lys Asn Lys Asn Ser Phe
100 105 110

Ser Val Leu Lys Lys Ile Leu Leu Asn Glu Asp Val Asn Ser Glu Glu
115 120 125

Leu Glu Ile Phe Arg Lys Asp Val Glu Ala Lys Leu Asn Lys Ile Asn
130 135 140

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

Asn Glu Asn Asn Val Glu Lys Val Gly Gly Lys Ser Lys Arg Asn Ile
165 170 175

Ile Tyr Asp Tyr Tyr Arg Glu Ser Ala Lys Arg Asn Asp Tyr Ile Asn
180 185 190

Asn Val Gln Glu Ala Phe Asp Lys Leu Tyr Lys Lys Glu Asp Ile Glu
195 200 205

Lys Leu Phe Phe Leu Ile Glu Asn Ser Lys Lys His Glu Lys Tyr Lys
210 215 220

Ile Arg Glu Tyr Tyr His Lys Ile Ile Gly Arg Lys Asn Asp Lys Glu
225 230 235 240

Asn Phe Ala Lys Ile Ile Tyr Glu Glu Ile Gln Asn Val Asn Asn Ile
245 250 255

Lys Glu Leu Ile Glu Lys Ile Pro Asp Met Ser Glu Leu Lys Lys Ser
260 265 270

Gln Val Phe Tyr Lys Tyr Tyr Leu Asp Lys Glu Glu Leu Asn Asp Lys
275 280 285

Asn Ile Lys Tyr Ala Phe Cys His Phe Val Glu Ile Glu Met Ser Gln
290 295 300

Leu Leu Lys Asn Tyr Val Tyr Lys Arg Leu Ser Asn Ile Ser Asn Asp
305 310 315 320

Lys Ile Lys Arg Ile Phe Glu Tyr Gln Asn Leu Lys Lys Leu Ile Glu
325 330 335

Asn Lys Leu Leu Asn Lys Leu Asp Thr Tyr Val Arg Asn Cys Gly Lys
340 345 350

Tyr Asn Tyr Tyr Leu Gln Val Gly Glu Ile Ala Thr Ser Asp Phe Ile
355 360 365

Ala Arg Asn Arg Gln Asn Glu Ala Phe Leu Arg Asn Ile Ile Gly Val
370 375 380

Ser Ser Val Ala Tyr Phe Ser Leu Arg Asn Ile Leu Glu Thr Glu Asn
385 390 395 400

Glu Asn Gly Ile Thr Gly Arg Met Arg Gly Lys Thr Val Lys Asn Asn
405 410 415

Lys Gly Glu Glu Lys Tyr Val Ser Gly Glu Val Asp Lys Ile Tyr Asn
420 425 430

Glu Asn Lys Gln Asn Glu Val Lys Glu Asn Leu Lys Met Phe Tyr Ser
435 440 445

Tyr Asp Phe Asn Met Asp Asn Lys Asn Glu Ile Glu Asp Phe Phe Ala
450 455 460

Asn Ile Asp Glu Ala Ile Ser Ser Ile Arg His Gly Ile Val His Phe
465 470 475 480

Asn Leu Glu Leu Glu Gly Lys Asp Ile Phe Ala Phe Lys Asn Ile Ala
485 490 495

Pro Ser Glu Ile Ser Lys Lys Met Phe Gln Asn Glu Ile Asn Glu Lys
500 505 510

Lys Leu Lys Leu Lys Ile Phe Lys Gln Leu Asn Ser Ala Asn Val Phe
515 520 525

Asn Tyr Tyr Glu Lys Asp Val Ile Ile Lys Tyr Leu Lys Asn Thr Lys
530 535 540

Phe Asn Phe Val Asn Lys Asn Ile Pro Phe Val Pro Ser Phe Thr Lys
545 550 555 560

Leu Tyr Asn Lys Ile Glu Asp Leu Arg Asn Thr Leu Lys Phe Phe Trp
565 570 575

Ser Val Pro Lys Asp Lys Glu Glu Lys Asp Ala Gln Ile Tyr Leu Leu
580 585 590

Lys Asn Ile Tyr Tyr Gly Glu Phe Leu Asn Lys Phe Val Lys Asn Ser
595 600 605

Lys Val Phe Phe Lys Ile Thr Asn Glu Val Ile Lys Ile Asn Lys Gln
610 615 620

Arg Asn Gln Lys Thr Gly His Tyr Lys Tyr Gln Lys Phe Glu Asn Ile
625 630 635 640

Glu Lys Thr Val Pro Val Glu Tyr Leu Ala Ile Ile Gln Ser Arg Glu
645 650 655

Met Ile Asn Asn Gln Asp Lys Glu Glu Lys Asn Thr Tyr Ile Asp Phe
660 665 670

Ile Gln Gln Ile Phe Leu Lys Gly Phe Ile Asp Tyr Leu Asn Lys Asn
675 680 685

Asn Leu Lys Tyr Ile Glu Ser Asn Asn Asn Asn Asp Asn Asn Asp Ile
690 695 700

Phe Ser Lys Ile Lys Ile Lys Lys Asp Asn Lys Glu Lys Tyr Asp Lys
705 710 715 720

Ile Leu Lys Asn Tyr Glu Lys His Asn Arg Asn Lys Glu Ile Pro His
725 730 735

Glu Ile Asn Glu Phe Val Arg Glu Ile Lys Leu Gly Lys Ile Leu Lys
740 745 750

Tyr Thr Glu Asn Leu Asn Met Phe Tyr Leu Ile Leu Lys Leu Leu Asn
755 760 765

His Lys Glu Leu Thr Asn Leu Lys Gly Ser Leu Glu Lys Tyr Gln Ser
770 775 780

Ala Asn Lys Glu Glu Thr Phe Ser Asp Glu Leu Glu Leu Ile Asn Leu
785 790 795 800

Leu Asn Leu Asp Asn Asn Arg Val Thr Glu Asp Phe Glu Leu Glu Ala
805 810 815

Asn Glu Ile Gly Lys Phe Leu Asp Phe Asn Glu Asn Lys Ile Lys Asp
820 825 830

Arg Lys Glu Leu Lys Lys Phe Asp Thr Asn Lys Ile Tyr Phe Asp Gly
835 840 845

Glu Asn Ile Ile Lys His Arg Ala Phe Tyr Asn Ile Lys Lys Tyr Gly
850 855 860

Met Leu Asn Leu Leu Glu Lys Ile Ala Asp Lys Ala Lys Tyr Lys Ile
865 870 875 880

Ser Leu Lys Glu Leu Lys Glu Tyr Ser Asn Lys Lys Asn Glu Ile Glu
885 890 895

Lys Asn Tyr Thr Met Gln Gln Asn Leu His Arg Lys Tyr Ala Arg Pro
900 905 910

Lys Lys Asp Glu Lys Phe Asn Asp Glu Asp Tyr Lys Glu Tyr Glu Lys
915 920 925

Ala Ile Gly Asn Ile Gln Lys Tyr Thr His Leu Lys Asn Lys Val Glu
930 935 940

Phe Asn Glu Leu Asn Leu Leu Gln Gly Leu Leu Leu Lys Ile Leu His
945 950 955 960

Arg Leu Val Gly Tyr Thr Ser Ile Trp Glu Arg Asp Leu Arg Phe Arg
965 970 975

Leu Lys Gly Glu Phe Pro Glu Asn His Tyr Ile Glu Glu Ile Phe Asn
980 985 990

Phe Asp Asn Ser Lys Asn Val Lys Tyr Lys Ser Gly Gln Ile Val Glu
995 1000 1005

Lys Tyr Ile Asn Phe Tyr Lys Glu Leu Tyr Lys Asp Asn Val Glu
1010 1015 1020

Lys Arg Ser Ile Tyr Ser Asp Lys Lys Val Lys Lys Leu Lys Gln
1025 1030 1035

Glu Lys Lys Asp Leu Tyr Ile Arg Asn Tyr Ile Ala His Phe Asn
1040 1045 1050

Tyr Ile Pro His Ala Glu Ile Ser Leu Leu Glu Val Leu Glu Asn
1055 1060 1065

Leu Arg Lys Leu Leu Ser Tyr Asp Arg Lys Leu Lys Asn Ala Ile
1070 1075 1080

Met Lys Ser Ile Val Asp Ile Leu Lys Glu Tyr Gly Phe Val Ala
1085 1090 1095

Thr Phe Lys Ile Gly Ala Asp Lys Lys Ile Glu Ile Gln Thr Leu
1100 1105 1110

Glu Ser Glu Lys Ile Val His Leu Lys Asn Leu Lys Lys Lys Lys
1115 1120 1125

Leu Met Thr Asp Arg Asn Ser Glu Glu Leu Cys Glu Leu Val Lys
1130 1135 1140

Val Met Phe Glu Tyr Lys Ala Leu Glu
1145 1150

<210> 22
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> LwaCas13a direct repeat

<400> 22
gatttagact accccaaaaa cgaaggggac taaaac 36

<210> 23
<211> 3363
<212> DNA
<213> Artificial Sequence

<220>
<223> LseCas13a nucleic acid sequence

<400> 23
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gaggtcgatc ggaagaaagt gctgatcagc cgggacaaga atggcgggaa actggtctat 180
gagaacgaaa tgcaggacaa tacagagcag atcatgcacc ataagaaaag ctcttctac 240
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 tga 3363

<210> 24
 <211> 1120
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> LseCas13a amino acid sequence

 <400> 24

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Phe Cys Asp Tyr Met Tyr Asn Arg Arg Glu Lys Lys Ile Ile Glu Val
 20 25 30

Lys Thr Met Arg Ile Thr Lys Val Glu Val Asp Arg Lys Lys Val Leu
 35 40 45

Ile Ser Arg Asp Lys Asn Gly Gly Lys Leu Val Tyr Glu Asn Glu Met
 50 55 60

Gln Asp Asn Thr Glu Gln Ile Met His His Lys Lys Ser Ser Phe Tyr
65 70 75 80

Lys Ser Val Val Asn Lys Thr Ile Cys Arg Pro Glu Gln Lys Gln Met
85 90 95

Lys Lys Leu Val His Gly Leu Leu Gln Glu Asn Ser Gln Glu Lys Ile
100 105 110

Lys Val Ser Asp Val Thr Lys Leu Asn Ile Ser Asn Phe Leu Asn His
115 120 125

Arg Phe Lys Lys Ser Leu Tyr Tyr Phe Pro Glu Asn Ser Pro Asp Lys
130 135 140

Ser Glu Glu Tyr Arg Ile Glu Ile Asn Leu Ser Gln Leu Leu Glu Asp
145 150 155 160

Ser Leu Lys Lys Gln Gln Gly Thr Phe Ile Cys Trp Glu Ser Phe Ser
165 170 175

Lys Asp Met Glu Leu Tyr Ile Asn Trp Ala Glu Asn Tyr Ile Ser Ser
180 185 190

Lys Thr Lys Leu Ile Lys Lys Ser Ile Arg Asn Asn Arg Ile Gln Ser
195 200 205

Thr Glu Ser Arg Ser Gly Gln Leu Met Asp Arg Tyr Met Lys Asp Ile
210 215 220

Leu Asn Lys Asn Lys Pro Phe Asp Ile Gln Ser Val Ser Glu Lys Tyr
225 230 235 240

Gln Leu Glu Lys Leu Thr Ser Ala Leu Lys Ala Thr Phe Lys Glu Ala
245 250 255

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

Asn His Glu Arg Gln Ile Ile Glu Glu Leu Lys Glu Asn Ser Glu Leu
275 280 285

Asn Gln Phe Asn Ile Glu Ile Arg Lys His Leu Glu Thr Tyr Phe Pro
290 295 300

Ile Lys Lys Thr Asn Arg Lys Val Gly Asp Ile Arg Asn Leu Glu Ile
305 310 315 320

Gly Glu Ile Gln Lys Ile Val Asn His Arg Leu Lys Asn Lys Ile Val
325 330 335

Gln Arg Ile Leu Gln Glu Gly Lys Leu Ala Ser Tyr Glu Ile Glu Ser
340 345 350

Thr Val Asn Ser Asn Ser Leu Gln Lys Ile Lys Ile Glu Glu Ala Phe
355 360 365

Ala Leu Lys Phe Ile Asn Ala Cys Leu Phe Ala Ser Asn Asn Leu Arg
370 375 380

Asn Met Val Tyr Pro Val Cys Lys Lys Asp Ile Leu Met Ile Gly Glu
385 390 395 400

Phe Lys Asn Ser Phe Lys Glu Ile Lys His Lys Lys Phe Ile Arg Gln
405 410 415

Trp Ser Gln Phe Phe Ser Gln Glu Ile Thr Val Asp Asp Ile Glu Leu
420 425 430

Ala Ser Trp Gly Leu Arg Gly Ala Ile Ala Pro Ile Arg Asn Glu Ile
435 440 445

Ile His Leu Lys Lys His Ser Trp Lys Lys Phe Phe Asn Asn Pro Thr
450 455 460

Phe Lys Val Lys Lys Ser Lys Ile Ile Asn Gly Lys Thr Lys Asp Val
465 470 475 480

Thr Ser Glu Phe Leu Tyr Lys Glu Thr Leu Phe Lys Asp Tyr Phe Tyr
485 490 495

Ser Glu Leu Asp Ser Val Pro Glu Leu Ile Ile Asn Lys Met Glu Ser
500 505 510

Ser Lys Ile Leu Asp Tyr Tyr Ser Ser Asp Gln Leu Asn Gln Val Phe
515 520 525

Thr Ile Pro Asn Phe Glu Leu Ser Leu Leu Thr Ser Ala Val Pro Phe
530 535 540

Ala Pro Ser Phe Lys Arg Val Tyr Leu Lys Gly Phe Asp Tyr Gln Asn
545 550 555 560

Gln Asp Glu Ala Gln Pro Asp Tyr Asn Leu Lys Leu Asn Ile Tyr Asn
565 570 575

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

Lys Met Val Tyr Tyr Gln Val Phe Leu Pro Gln Phe Thr Thr Asn Asn
595 600 605

Asp Leu Phe Lys Ser Ser Val Asp Phe Ile Leu Thr Leu Asn Lys Glu
610 615 620

Arg Lys Gly Tyr Ala Lys Ala Phe Gln Asp Ile Arg Lys Met Asn Lys
625 630 635 640

Asp Glu Lys Pro Ser Glu Tyr Met Ser Tyr Ile Gln Ser Gln Leu Met
645 650 655

Leu Tyr Gln Lys Lys Gln Glu Glu Lys Glu Lys Ile Asn His Phe Glu
660 665 670

Lys Phe Ile Asn Gln Val Phe Ile Lys Gly Phe Asn Ser Phe Ile Glu
675 680 685

Lys Asn Arg Leu Thr Tyr Ile Cys His Pro Thr Lys Asn Thr Val Pro
690 695 700

Glu Asn Asp Asn Ile Glu Ile Pro Phe His Thr Asp Met Asp Asp Ser
705 710 715 720

Asn Ile Ala Phe Trp Leu Met Cys Lys Leu Leu Asp Ala Lys Gln Leu
725 730 735

Ser Glu Leu Arg Asn Glu Met Ile Lys Phe Ser Cys Ser Leu Gln Ser
740 745 750

Thr Glu Glu Ile Ser Thr Phe Thr Lys Ala Arg Glu Val Ile Gly Leu
755 760 765

Ala Leu Leu Asn Gly Glu Lys Gly Cys Asn Asp Trp Lys Glu Leu Phe
770 775 780

Asp Asp Lys Glu Ala Trp Lys Lys Asn Met Ser Leu Tyr Val Ser Glu
785 790 795 800

Glu Leu Leu Gln Ser Leu Pro Tyr Thr Gln Glu Asp Gly Gln Thr Pro
805 810 815

Val Ile Asn Arg Ser Ile Asp Leu Val Lys Lys Tyr Gly Thr Glu Thr
820 825 830

Ile Leu Glu Lys Leu Phe Ser Ser Ser Asp Asp Tyr Lys Val Ser Ala
835 840 845

Lys Asp Ile Ala Lys Leu His Glu Tyr Asp Val Thr Glu Lys Ile Ala
850 855 860

Gln Gln Glu Ser Leu His Lys Gln Trp Ile Glu Lys Pro Gly Leu Ala
865 870 875 880

Arg Asp Ser Ala Trp Thr Lys Lys Tyr Gln Asn Val Ile Asn Asp Ile
885 890 895

Ser Asn Tyr Gln Trp Ala Lys Thr Lys Val Glu Leu Thr Gln Val Arg
900 905 910

His Leu His Gln Leu Thr Ile Asp Leu Leu Ser Arg Leu Ala Gly Tyr
915 920 925

Met Ser Ile Ala Asp Arg Asp Phe Gln Phe Ser Ser Asn Tyr Ile Leu
930 935 940

Glu Arg Glu Asn Ser Glu Tyr Arg Val Thr Ser Trp Ile Leu Leu Ser
945 950 955 960

Glu Asn Lys Asn Lys Asn Lys Tyr Asn Asp Tyr Glu Leu Tyr Asn Leu
965 970 975

Lys Asn Ala Ser Ile Lys Val Ser Ser Lys Asn Asp Pro Gln Leu Lys
980 985 990

Val Asp Leu Lys Gln Leu Arg Leu Thr Leu Glu Tyr Leu Glu Leu Phe
995 1000 1005

Asp Asn Arg Leu Lys Glu Lys Arg Asn Asn Ile Ser His Phe Asn
1010 1015 1020

Tyr Leu Asn Gly Gln Leu Gly Asn Ser Ile Leu Glu Leu Phe Asp
1025 1030 1035

Asp Ala Arg Asp Val Leu Ser Tyr Asp Arg Lys Leu Lys Asn Ala
1040 1045 1050

Val Ser Lys Ser Leu Lys Glu Ile Leu Ser Ser His Gly Met Glu
1055 1060 1065

Val Thr Phe Lys Pro Leu Tyr Gln Thr Asn His His Leu Lys Ile
1070 1075 1080

Asp Lys Leu Gln Pro Lys Lys Ile His His Leu Gly Glu Lys Ser
1085 1090 1095

Thr Val Ser Ser Asn Gln Val Ser Asn Glu Tyr Cys Gln Leu Val
1100 1105 1110

Arg Thr Leu Leu Thr Met Lys
1115 1120

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<211> 36

<212> DNA
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<220>
<223> LseCas13a direct repeat

<400> 25
gtaagagact acctctatat gaaagaggac taaaac 36

<210> 26
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<212> DNA
<213> Artificial Sequence

<220>
<223> LbmCas13a nucleic acid sequence

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gcaaagaggg ccaacgatac caaggtgctg ttcaacgtgt tcaacacaaa ggacctgtac 180
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aagatcagca gaggctccaa taccaggtcc tctaaccagt ctaagtacaa caacaagagc	3960
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tga	4023

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 <212> PRT
 <213> Artificial Sequence
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<223> LbmCas13a amino acid sequence

<400> 27

Met Gln Ile Ser Lys Val Asn His Lys His Val Ala Val Gly Gln Lys
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Asp Arg Glu Arg Ile Thr Gly Phe Ile Tyr Asn Asp Pro Val Gly Asp
20 25 30

Glu Lys Ser Leu Glu Asp Val Val Ala Lys Arg Ala Asn Asp Thr Lys
35 40 45

Val Leu Phe Asn Val Phe Asn Thr Lys Asp Leu Tyr Asp Ser Gln Glu
50 55 60

Ser Asp Lys Ser Glu Lys Asp Lys Glu Ile Ile Ser Lys Gly Ala Lys
65 70 75 80

Phe Val Ala Lys Ser Phe Asn Ser Ala Ile Thr Ile Leu Lys Lys Gln
85 90 95

Asn Lys Ile Tyr Ser Thr Leu Thr Ser Gln Gln Val Ile Lys Glu Leu
100 105 110

Lys Asp Lys Phe Gly Gly Ala Arg Ile Tyr Asp Asp Asp Ile Glu Glu
115 120 125

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

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

Leu Ser Lys Asp Glu Glu Glu Leu Ile Gln Glu Tyr Phe Val Lys Gln
165 170 175

Leu Val Glu Glu Tyr Thr Lys Thr Lys Leu Gln Lys Asn Val Val Lys
180 185 190

Ser Ile Lys Asn Gln Asn Met Val Ile Gln Pro Asp Ser Asp Ser Gln
195 200 205

Val Leu Ser Leu Ser Glu Ser Arg Arg Glu Lys Gln Ser Ser Ala Val
210 215 220

Ser Ser Asp Thr Leu Val Asn Cys Lys Glu Lys Asp Val Leu Lys Ala
225 230 235 240

Phe Leu Thr Asp Tyr Ala Val Leu Asp Glu Asp Glu Arg Asn Ser Leu
245 250 255

Leu Trp Lys Leu Arg Asn Leu Val Asn Leu Tyr Phe Tyr Gly Ser Glu
260 265 270

Ser Ile Arg Asp Tyr Ser Tyr Thr Lys Glu Lys Ser Val Trp Lys Glu
275 280 285

His Asp Glu Gln Lys Ala Asn Lys Thr Leu Phe Ile Asp Glu Ile Cys
290 295 300

His Ile Thr Lys Ile Gly Lys Asn Gly Lys Glu Gln Lys Val Leu Asp
305 310 315 320

Tyr Glu Glu Asn Arg Ser Arg Cys Arg Lys Gln Asn Ile Asn Tyr Tyr
325 330 335

Arg Ser Ala Leu Asn Tyr Ala Lys Asn Asn Thr Ser Gly Ile Phe Glu
340 345 350

Asn Glu Asp Ser Asn His Phe Trp Ile His Leu Ile Glu Asn Glu Val
355 360 365

Glu Arg Leu Tyr Asn Gly Ile Glu Asn Gly Glu Glu Phe Lys Phe Glu
370 375 380

Thr Gly Tyr Ile Ser Glu Lys Val Trp Lys Ala Val Ile Asn His Leu
385 390 395 400

Ser Ile Lys Tyr Ile Ala Leu Gly Lys Ala Val Tyr Asn Tyr Ala Met
405 410 415

Lys Glu Leu Ser Ser Pro Gly Asp Ile Glu Pro Gly Lys Ile Asp Asp
420 425 430

Ser Tyr Ile Asn Gly Ile Thr Ser Phe Asp Tyr Glu Ile Ile Lys Ala
435 440 445

Glu Glu Ser Leu Gln Arg Asp Ile Ser Met Asn Val Val Phe Ala Thr
450 455 460

Asn Tyr Leu Ala Cys Ala Thr Val Asp Thr Asp Lys Asp Phe Leu Leu
465 470 475 480

Phe Ser Lys Glu Asp Ile Arg Ser Cys Thr Lys Lys Asp Gly Asn Leu
485 490 495

Cys Lys Asn Ile Met Gln Phe Trp Gly Gly Tyr Ser Thr Trp Lys Asn
500 505 510

Phe Cys Glu Glu Tyr Leu Lys Asp Asp Lys Asp Ala Leu Glu Leu Leu
515 520 525

Tyr Ser Leu Lys Ser Met Leu Tyr Ser Met Arg Asn Ser Ser Phe His
530 535 540

Phe Ser Thr Glu Asn Val Asp Asn Gly Ser Trp Asp Thr Glu Leu Ile
545 550 555 560

Gly Lys Leu Phe Glu Glu Asp Cys Asn Arg Ala Ala Arg Ile Glu Lys
565 570 575

Glu Lys Phe Tyr Asn Asn Asn Leu His Met Phe Tyr Ser Ser Ser Leu
580 585 590

Leu Glu Lys Val Leu Glu Arg Leu Tyr Ser Ser His His Glu Arg Ala
595 600 605

Ser Gln Val Pro Ser Phe Asn Arg Val Phe Val Arg Lys Asn Phe Pro
610 615 620

Ser Ser Leu Ser Glu Gln Arg Ile Thr Pro Lys Phe Thr Asp Ser Lys
625 630 635 640

Asp Glu Gln Ile Trp Gln Ser Ala Val Tyr Tyr Leu Cys Lys Glu Ile
645 650 655

Tyr Tyr Asn Asp Phe Leu Gln Ser Lys Glu Ala Tyr Lys Leu Phe Arg
660 665 670

Glu Gly Val Lys Asn Leu Asp Lys Asn Asp Ile Asn Asn Gln Lys Ala
675 680 685

Ala Asp Ser Phe Lys Gln Ala Val Val Tyr Tyr Gly Lys Ala Ile Gly
690 695 700

Asn Ala Thr Leu Ser Gln Val Cys Gln Ala Ile Met Thr Glu Tyr Asn
705 710 715 720

Arg Gln Asn Asn Asp Gly Leu Lys Lys Lys Ser Ala Tyr Ala Glu Lys
725 730 735

Gln Asn Ser Asn Lys Tyr Lys His Tyr Pro Leu Phe Leu Lys Gln Val
740 745 750

Leu Gln Ser Ala Phe Trp Glu Tyr Leu Asp Glu Asn Lys Glu Ile Tyr
755 760 765

Gly Phe Ile Ser Ala Gln Ile His Lys Ser Asn Val Glu Ile Lys Ala
770 775 780

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

Asp Lys Val Lys Lys Thr Pro Glu Leu Gln Lys Trp Tyr Thr Leu Gly
805 810 815

Arg Leu Ile Asn Pro Arg Gln Ala Asn Gln Phe Leu Gly Ser Ile Arg
820 825 830

Asn Tyr Val Gln Phe Val Lys Asp Ile Gln Arg Arg Ala Lys Glu Asn
835 840 845

Gly Asn Pro Ile Arg Asn Tyr Tyr Glu Val Leu Glu Ser Asp Ser Ile
850 855 860

Ile Lys Ile Leu Glu Met Cys Thr Lys Leu Asn Gly Thr Thr Ser Asn
865 870 875 880

Asp Ile His Asp Tyr Phe Arg Asp Glu Asp Glu Tyr Ala Glu Tyr Ile
885 890 895

Ser Gln Phe Val Asn Phe Gly Asp Val His Ser Gly Ala Ala Leu Asn
900 905 910

Ala Phe Cys Asn Ser Glu Ser Glu Gly Lys Lys Asn Gly Ile Tyr Tyr
915 920 925

Asp Gly Ile Asn Pro Ile Val Asn Arg Asn Trp Val Leu Cys Lys Leu
930 935 940

Tyr Gly Ser Pro Asp Leu Ile Ser Lys Ile Ile Ser Arg Val Asn Glu
945 950 955 960

Asn Met Ile His Asp Phe His Lys Gln Glu Asp Leu Ile Arg Glu Tyr
965 970 975

Gln Ile Lys Gly Ile Cys Ser Asn Lys Lys Glu Gln Gln Asp Leu Arg
980 985 990

Thr Phe Gln Val Leu Lys Asn Arg Val Glu Leu Arg Asp Ile Val Glu
995 1000 1005

Tyr Ser Glu Ile Ile Asn Glu Leu Tyr Gly Gln Leu Ile Lys Trp
1010 1015 1020

Cys Tyr Leu Arg Glu Arg Asp Leu Met Tyr Phe Gln Leu Gly Phe
1025 1030 1035

His Tyr Leu Cys Leu Asn Asn Ala Ser Ser Lys Glu Ala Asp Tyr
1040 1045 1050

Ile Lys Ile Asn Val Asp Asp Arg Asn Ile Ser Gly Ala Ile Leu
1055 1060 1065

Tyr Gln Ile Ala Ala Met Tyr Ile Asn Gly Leu Pro Val Tyr Tyr
1070 1075 1080

Lys Lys Asp Asp Met Tyr Val Ala Leu Lys Ser Gly Lys Lys Ala
1085 1090 1095

Ser Asp Glu Leu Asn Ser Asn Glu Gln Thr Ser Lys Lys Ile Asn
1100 1105 1110

Tyr Phe Leu Lys Tyr Gly Asn Asn Ile Leu Gly Asp Lys Lys Asp
1115 1120 1125

Gln Leu Tyr Leu Ala Gly Leu Glu Leu Phe Glu Asn Val Ala Glu
1130 1135 1140

His Glu Asn Ile Ile Ile Phe Arg Asn Glu Ile Asp His Phe His
1145 1150 1155

Tyr Phe Tyr Asp Arg Asp Arg Ser Met Leu Asp Leu Tyr Ser Glu
1160 1165 1170

Val Phe Asp Arg Phe Phe Thr Tyr Asp Met Lys Leu Arg Lys Asn
1175 1180 1185

Val Val Asn Met Leu Tyr Asn Ile Leu Leu Asp His Asn Ile Val
1190 1195 1200

Ser Ser Phe Val Phe Glu Thr Gly Glu Lys Lys Val Gly Arg Gly
1205 1210 1215

Asp Ser Glu Val Ile Lys Pro Ser Ala Lys Ile Arg Leu Arg Ala
1220 1225 1230

Asn Asn Gly Val Ser Ser Asp Val Phe Thr Tyr Lys Val Gly Ser
1235 1240 1245

Lys Asp Glu Leu Lys Ile Ala Thr Leu Pro Ala Lys Asn Glu Glu
1250 1255 1260

Phe Leu Leu Asn Val Ala Arg Leu Ile Tyr Tyr Pro Asp Met Glu
1265 1270 1275

Ala Val Ser Glu Asn Met Val Arg Glu Gly Val Val Lys Val Glu
1280 1285 1290

Lys Ser Asn Asp Lys Lys Gly Lys Ile Ser Arg Gly Ser Asn Thr
1295 1300 1305

Arg Ser Ser Asn Gln Ser Lys Tyr Asn Asn Lys Ser Lys Asn Arg
1310 1315 1320

Met Asn Tyr Ser Met Gly Ser Ile Phe Glu Lys Met Asp Leu Lys
1325 1330 1335

Phe Asp
1340

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<223> LbnCas13a nucleic acid sequence

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<212> PRT

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<223> LbnCas13a amino acid sequence

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          20           25           30

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Ile Leu Tyr Asn Asp Pro Ser Arg Tyr Gly Lys Ser Arg Lys Asn Asp
          35           40           45

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Glu Asp Arg Asp Arg Tyr Ile Glu Ser Arg Leu Lys Ser Ser Gly Lys
          50           55           60

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Leu Tyr Arg Ile Phe Asn Glu Asp Lys Asn Lys Arg Glu Thr Asp Glu
65 70 75 80

Leu Gln Trp Phe Leu Ser Glu Ile Val Lys Lys Ile Asn Arg Arg Asn
85 90 95

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

Lys Ala Phe Glu Lys Tyr Ala Glu Leu Ser Tyr Thr Asn Arg Arg Asn
115 120 125

Lys Val Ser Gly Ser Pro Ala Phe Glu Thr Cys Gly Val Asp Ala Ala
130 135 140

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

Arg Ile Lys Asn Asn Ile Asp Asn Lys Val Ser Glu Asp Ile Ile Asp
165 170 175

Arg Ile Ile Ala Lys Tyr Leu Lys Lys Ser Leu Cys Arg Glu Arg Val
180 185 190

Lys Arg Gly Leu Lys Lys Leu Leu Met Asn Ala Phe Asp Leu Pro Tyr
195 200 205

Ser Asp Pro Asp Ile Asp Val Gln Arg Asp Phe Ile Asp Tyr Val Leu
210 215 220

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

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245 250 255

Ile Thr Val Ser Lys Gly Gly Thr Glu Ser Gly Asn Lys Arg Ser Ala
260 265 270

Glu Lys Glu Ala Phe Lys Lys Phe Leu Ser Asp Tyr Ala Ser Leu Asp
275 280 285

Glu Arg Val Arg Asp Asp Met Leu Arg Arg Met Arg Arg Leu Val Val
290 295 300

Leu Tyr Phe Tyr Gly Ser Asp Asp Ser Lys Leu Ser Asp Val Asn Glu
305 310 315 320

Lys Phe Asp Val Trp Glu Asp His Ala Ala Arg Arg Val Asp Asn Arg
325 330 335

Glu Phe Ile Lys Leu Pro Leu Glu Asn Lys Leu Ala Asn Gly Lys Thr
340 345 350

Asp Lys Asp Ala Glu Arg Ile Arg Lys Asn Thr Val Lys Glu Leu Tyr
355 360 365

Arg Asn Gln Asn Ile Gly Cys Tyr Arg Gln Ala Val Lys Ala Val Glu
370 375 380

Glu Asp Asn Asn Gly Arg Tyr Phe Asp Asp Lys Met Leu Asn Met Phe
385 390 395 400

Phe Ile His Arg Ile Glu Tyr Gly Val Glu Lys Ile Tyr Ala Asn Leu
405 410 415

Lys Gln Val Thr Glu Phe Lys Ala Arg Thr Gly Tyr Leu Ser Glu Lys
420 425 430

Ile Trp Lys Asp Leu Ile Asn Tyr Ile Ser Ile Lys Tyr Ile Ala Met
435 440 445

Gly Lys Ala Val Tyr Asn Tyr Ala Met Asp Glu Leu Asn Ala Ser Asp
450 455 460

Lys Lys Glu Ile Glu Leu Gly Lys Ile Ser Glu Glu Tyr Leu Ser Gly
465 470 475 480

Ile Ser Ser Phe Asp Tyr Glu Leu Ile Lys Ala Glu Glu Met Leu Gln
485 490 495

Arg Glu Thr Ala Val Tyr Val Ala Phe Ala Ala Arg His Leu Ser Ser
500 505 510

Gln Thr Val Glu Leu Asp Ser Glu Asn Ser Asp Phe Leu Leu Leu Lys
515 520 525

Pro Lys Gly Thr Met Asp Lys Asn Asp Lys Asn Lys Leu Ala Ser Asn
530 535 540

Asn Ile Leu Asn Phe Leu Lys Asp Lys Glu Thr Leu Arg Asp Thr Ile
545 550 555 560

Leu Gln Tyr Phe Gly Gly His Ser Leu Trp Thr Asp Phe Pro Phe Asp
565 570 575

Lys Tyr Leu Ala Gly Gly Lys Asp Asp Val Asp Phe Leu Thr Asp Leu
580 585 590

Lys Asp Val Ile Tyr Ser Met Arg Asn Asp Ser Phe His Tyr Ala Thr
595 600 605

Glu Asn His Asn Asn Gly Lys Trp Asn Lys Glu Leu Ile Ser Ala Met
610 615 620

Phe Glu His Glu Thr Glu Arg Met Thr Val Val Met Lys Asp Lys Phe
625 630 635 640

Tyr Ser Asn Asn Leu Pro Met Phe Tyr Lys Asn Asp Asp Leu Lys Lys
645 650 655

Leu Leu Ile Asp Leu Tyr Lys Asp Asn Val Glu Arg Ala Ser Gln Val
660 665 670

Pro Ser Phe Asn Lys Val Phe Val Arg Lys Asn Phe Pro Ala Leu Val
675 680 685

Arg Asp Lys Asp Asn Leu Gly Ile Glu Leu Asp Leu Lys Ala Asp Ala
690 695 700

Asp Lys Gly Glu Asn Glu Leu Lys Phe Tyr Asn Ala Leu Tyr Tyr Met
705 710 715 720

Phe Lys Glu Ile Tyr Tyr Asn Ala Phe Leu Asn Asp Lys Asn Val Arg
725 730 735

Glu Arg Phe Ile Thr Lys Ala Thr Lys Val Ala Asp Asn Tyr Asp Arg
740 745 750

Asn Lys Glu Arg Asn Leu Lys Asp Arg Ile Lys Ser Ala Gly Ser Asp
755 760 765

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

Asp Phe Gly Gln Arg Ile Lys Asn Ile Val Gln Val Asn Pro Asp Tyr
785 790 795 800

Thr Leu Ala Gln Ile Cys Gln Leu Ile Met Thr Glu Tyr Asn Gln Gln
805 810 815

Asn Asn Gly Cys Met Gln Lys Lys Ser Ala Ala Arg Lys Asp Ile Asn
820 825 830

Lys Asp Ser Tyr Gln His Tyr Lys Met Leu Leu Leu Val Asn Leu Arg
835 840 845

Lys Ala Phe Leu Glu Phe Ile Lys Glu Asn Tyr Ala Phe Val Leu Lys
850 855 860

Pro Tyr Lys His Asp Leu Cys Asp Lys Ala Asp Phe Val Pro Asp Phe
865 870 875 880

Ala Lys Tyr Val Lys Pro Tyr Ala Gly Leu Ile Ser Arg Val Ala Gly
885 890 895

Ser Ser Glu Leu Gln Lys Trp Tyr Ile Val Ser Arg Phe Leu Ser Pro
900 905 910

Ala Gln Ala Asn His Met Leu Gly Phe Leu His Ser Tyr Lys Gln Tyr
915 920 925

Val Trp Asp Ile Tyr Arg Arg Ala Ser Glu Thr Gly Thr Glu Ile Asn
930 935 940

His Ser Ile Ala Glu Asp Lys Ile Ala Gly Val Asp Ile Thr Asp Val
945 950 955 960

Asp Ala Val Ile Asp Leu Ser Val Lys Leu Cys Gly Thr Ile Ser Ser
965 970 975

Glu Ile Ser Asp Tyr Phe Lys Asp Asp Glu Val Tyr Ala Glu Tyr Ile
980 985 990

Ser Ser Tyr Leu Asp Phe Glu Tyr Asp Gly Gly Asn Tyr Lys Asp Ser
995 1000 1005

Leu Asn Arg Phe Cys Asn Ser Asp Ala Val Asn Asp Gln Lys Val
1010 1015 1020

Ala Leu Tyr Tyr Asp Gly Glu His Pro Lys Leu Asn Arg Asn Ile
1025 1030 1035

Ile Leu Ser Lys Leu Tyr Gly Glu Arg Arg Phe Leu Glu Lys Ile
1040 1045 1050

Thr Asp Arg Val Ser Arg Ser Asp Ile Val Glu Tyr Tyr Lys Leu
1055 1060 1065

Lys Lys Glu Thr Ser Gln Tyr Gln Thr Lys Gly Ile Phe Asp Ser
1070 1075 1080

Glu Asp Glu Gln Lys Asn Ile Lys Lys Phe Gln Glu Met Lys Asn
1085 1090 1095

Ile Val Glu Phe Arg Asp Leu Met Asp Tyr Ser Glu Ile Ala Asp
1100 1105 1110

Glu Leu Gln Gly Gln Leu Ile Asn Trp Ile Tyr Leu Arg Glu Arg
1115 1120 1125

Asp Leu Met Asn Phe Gln Leu Gly Tyr His Tyr Ala Cys Leu Asn
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Asn Asp Ser Asn Lys Gln Ala Thr Tyr Val Thr Leu Asp Tyr Gln
1145 1150 1155

Gly Lys Lys Asn Arg Lys Ile Asn Gly Ala Ile Leu Tyr Gln Ile
1160 1165 1170

Cys Ala Met Tyr Ile Asn Gly Leu Pro Leu Tyr Tyr Val Asp Lys
1175 1180 1185

Asp Ser Ser Glu Trp Thr Val Ser Asp Gly Lys Glu Ser Thr Gly
1190 1195 1200

Ala Lys Ile Gly Glu Phe Tyr Arg Tyr Ala Lys Ser Phe Glu Asn
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Thr Ser Asp Cys Tyr Ala Ser Gly Leu Glu Ile Phe Glu Asn Ile
1220 1225 1230

Ser Glu His Asp Asn Ile Thr Glu Leu Arg Asn Tyr Ile Glu His
1235 1240 1245

Phe Arg Tyr Tyr Ser Ser Phe Asp Arg Ser Phe Leu Gly Ile Tyr
1250 1255 1260

Ser Glu Val Phe Asp Arg Phe Phe Thr Tyr Asp Leu Lys Tyr Arg
1265 1270 1275

Lys Asn Val Pro Thr Ile Leu Tyr Asn Ile Leu Leu Gln His Phe
1280 1285 1290

Val Asn Val Arg Phe Glu Phe Val Ser Gly Lys Lys Met Ile Gly
1295 1300 1305

Ile Asp Lys Lys Asp Arg Lys Ile Ala Lys Glu Lys Glu Cys Ala
1310 1315 1320

Arg Ile Thr Ile Arg Glu Lys Asn Gly Val Tyr Ser Glu Gln Phe
1325 1330 1335

Thr Tyr Lys Leu Lys Asn Gly Thr Val Tyr Val Asp Ala Arg Asp
1340 1345 1350

Lys Arg Tyr Leu Gln Ser Ile Ile Arg Leu Leu Phe Tyr Pro Glu
1355 1360 1365

Lys Val Asn Met Asp Glu Met Ile Glu Val Lys Glu Lys Lys Lys
1370 1375 1380

Pro Ser Asp Asn Asn Thr Gly Lys Gly Tyr Ser Lys Arg Asp Arg
1385 1390 1395

Gln Gln Asp Arg Lys Glu Tyr Asp Lys Tyr Lys Glu Lys Lys Lys
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Lys Glu Gly Asn Phe Leu Ser Gly Met Gly Gly Asn Ile Asn Trp
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Asp Glu Ile Asn Ala Gln Leu Lys Asn
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aggtttgatc agctgaacgt gaaggccaag cgcctgtata acgtgttcaa tcagtccaag 180

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<212> PRT
<213> Artificial Sequence

<220>
<223> CamCas13a amino acid sequence

<400> 33

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Gln Glu Val Asn Asp Leu Asp Lys Arg Phe Asp Gln Leu Asn Val Lys
35 40 45

Ala Lys Arg Leu Tyr Asn Val Phe Asn Gln Ser Lys Ala Glu Glu Asp
50 55 60

Asp Asp Glu Lys Arg Phe Gly Lys Val Val Lys Lys Leu Asn Arg Glu
65 70 75 80

Leu Lys Asp Leu Leu Phe His Arg Glu Val Ser Arg Tyr Asn Ser Ile
85 90 95

Gly Asn Ala Lys Tyr Asn Tyr Tyr Gly Ile Lys Ser Asn Pro Glu Glu
100 105 110

Ile Val Ser Asn Leu Gly Met Val Glu Ser Leu Lys Gly Glu Arg Asp
115 120 125

Pro Gln Lys Val Ile Ser Lys Leu Leu Leu Tyr Tyr Leu Arg Lys Gly
130 135 140

Leu Lys Pro Gly Thr Asp Gly Leu Arg Met Ile Leu Glu Ala Ser Cys
145 150 155 160

Gly Leu Arg Lys Leu Ser Gly Asp Glu Lys Glu Leu Lys Val Phe Leu
165 170 175

Gln Thr Leu Asp Glu Asp Phe Glu Lys Lys Thr Phe Lys Lys Asn Leu
180 185 190

Ile Arg Ser Ile Glu Asn Gln Asn Met Ala Val Gln Pro Ser Asn Glu
195 200 205

Gly Asp Pro Ile Ile Gly Ile Thr Gln Gly Arg Phe Asn Ser Gln Lys
210 215 220

Asn Glu Glu Lys Ser Ala Ile Glu Arg Met Met Ser Met Tyr Ala Asp
225 230 235 240

Leu Asn Glu Asp His Arg Glu Asp Val Leu Arg Lys Leu Arg Arg Leu
245 250 255

Asn Val Leu Tyr Phe Asn Val Asp Thr Glu Lys Thr Glu Glu Pro Thr
260 265 270

Leu Pro Gly Glu Val Asp Thr Asn Pro Val Phe Glu Val Trp His Asp
275 280 285

His Glu Lys Gly Lys Glu Asn Asp Arg Gln Phe Ala Thr Phe Ala Lys
290 295 300

Ile Leu Thr Glu Asp Arg Glu Thr Arg Lys Lys Glu Lys Leu Ala Val
305 310 315 320

Lys Glu Ala Leu Asn Asp Leu Lys Ser Ala Ile Arg Asp His Asn Ile
325 330 335

Met Ala Tyr Arg Cys Ser Ile Lys Val Thr Glu Gln Asp Lys Asp Gly
340 345 350

Leu Phe Phe Glu Asp Gln Arg Ile Asn Arg Phe Trp Ile His His Ile
355 360 365

Glu Ser Ala Val Glu Arg Ile Leu Ala Ser Ile Asn Pro Glu Lys Leu
370 375 380

Tyr Lys Leu Arg Ile Gly Tyr Leu Gly Glu Lys Val Trp Lys Asp Leu
385 390 395 400

Leu Asn Tyr Leu Ser Ile Lys Tyr Ile Ala Val Gly Lys Ala Val Phe
405 410 415

His Phe Ala Met Glu Asp Leu Gly Lys Thr Gly Gln Asp Ile Glu Leu
420 425 430

Gly Lys Leu Ser Asn Ser Val Ser Gly Gly Leu Thr Ser Phe Asp Tyr
435 440 445

Glu Gln Ile Arg Ala Asp Glu Thr Leu Gln Arg Gln Leu Ser Val Glu
450 455 460

Val Ala Phe Ala Ala Asn Asn Leu Phe Arg Ala Val Val Gly Gln Thr
465 470 475 480

Gly Lys Lys Ile Glu Gln Ser Lys Ser Glu Glu Asn Glu Glu Asp Phe
485 490 495

Leu Leu Trp Lys Ala Glu Lys Ile Ala Glu Ser Ile Lys Lys Glu Gly
500 505 510

Glu Gly Asn Thr Leu Lys Ser Ile Leu Gln Phe Phe Gly Gly Ala Ser
515 520 525

Ser Trp Asp Leu Asn His Phe Cys Ala Ala Tyr Gly Asn Glu Ser Ser
530 535 540

Ala Leu Gly Tyr Glu Thr Lys Phe Ala Asp Asp Leu Arg Lys Ala Ile
545 550 555 560

Tyr Ser Leu Arg Asn Glu Thr Phe His Phe Thr Thr Leu Asn Lys Gly
565 570 575

Ser Phe Asp Trp Asn Ala Lys Leu Ile Gly Asp Met Phe Ser His Glu
580 585 590

Ala Ala Thr Gly Ile Ala Val Glu Arg Thr Arg Phe Tyr Ser Asn Asn
595 600 605

Leu Pro Met Phe Tyr Arg Glu Ser Asp Leu Lys Arg Ile Met Asp His
610 615 620

Leu Tyr Asn Thr Tyr His Pro Arg Ala Ser Gln Val Pro Ser Phe Asn
625 630 635 640

Ser Val Phe Val Arg Lys Asn Phe Arg Leu Phe Leu Ser Asn Thr Leu
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Asn Thr Asn Thr Ser Phe Asp Thr Glu Val Tyr Gln Lys Trp Glu Ser
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Gly Val Tyr Tyr Leu Phe Lys Glu Ile Tyr Tyr Asn Ser Phe Leu Pro
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Ser Gly Asp Ala His His Leu Phe Phe Glu Gly Leu Arg Arg Ile Arg
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Lys Glu Ala Asp Asn Leu Pro Ile Val Gly Lys Glu Ala Lys Lys Arg
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Asn Ala Val Gln Asp Phe Gly Arg Arg Cys Asp Glu Leu Lys Asn Leu
725 730 735

Ser Leu Ser Ala Ile Cys Gln Met Ile Met Thr Glu Tyr Asn Glu Gln
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Asn Asn Gly Asn Arg Lys Val Lys Ser Thr Arg Glu Asp Lys Arg Lys
755 760 765

Pro Asp Ile Phe Gln His Tyr Lys Met Leu Leu Leu Arg Thr Leu Gln
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Glu Ala Phe Ala Ile Tyr Ile Arg Arg Glu Glu Phe Lys Phe Ile Phe
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820 825 830

Gln Ser Pro Asp Leu Gln Arg Trp Tyr Val Leu Cys Lys Phe Leu Asn
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Ala Leu Lys Thr Phe Cys Asn Glu Glu Glu Val Lys Ala Gly Ile Tyr
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Asp Gly Lys Lys Asn Ile Ser Thr Cys Met Ile Ala Ala Arg Asp
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Gln Lys Tyr Leu Asn Thr Val Ala Arg Leu Leu Tyr Tyr Pro His
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Pro Tyr Arg Glu Tyr Lys Asn Lys Phe Ile Glu Arg Lys Ile Ile Leu
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Gly Met Lys Asp Arg Glu Ser Glu Leu Ile Pro Phe Gly Glu Gln Thr
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675 680 685

Val Arg Lys Ala Glu Lys Asn Asp Lys Gly Phe Glu Lys Asn Ile Thr
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Met Asn Phe Glu Lys Leu Leu Met Gln Ile Phe Val Lys Gly Phe Asp
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740 745 750

Glu Arg Glu Lys Thr Leu Lys Ala Ser Ile Gln Val Glu His Gln Leu
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Val Ala Thr Asn Ser Ala Ile Ser Tyr Trp Leu Phe Cys Lys Leu Leu
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Asp Ser Arg His Leu Asn Glu Leu Arg Asn Glu Met Ile Lys Phe Lys
785 790 795 800

Gln Ser Arg Ile Lys Phe Asn His Thr Gln His Ala Glu Leu Ile Gln
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Asn Leu Leu Pro Ile Val Glu Leu Thr Ile Leu Ser Asn Asp Tyr Asp
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Glu Lys Asn Asp Ser Gln Asn Val Asp Val Ser Ala Tyr Phe Glu Asp
835 840 845

Lys Ser Leu Tyr Glu Thr Ala Pro Tyr Val Gln Thr Asp Asp Arg Thr
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Gln Thr Leu Gly Ala Glu Lys Arg Glu Glu Tyr Arg Asp Tyr Cys Lys
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Gly Phe Ser Ala Leu Phe Glu Arg Asp Leu Val Tyr Phe Ser Arg Ser
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Ile Lys Asn Ile Lys Val Ile Asp Asn Glu Glu Asn Pro Tyr Lys
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ttcgagattg agagcctgaa gcctaagaag atcatccacc tggagaagtc caaccactct	3600
ttccctatgg accaggtgtc ccaggagtac tgtgatctgg tgaagaagat gctgggtgtt	3660
accaattga	3669

<210> 39
 <211> 1222
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Cga2Cas13a amino acid sequence

<400> 39

Met Ile Leu Lys Leu Lys Ile Asp Glu Asn His Lys Asn Phe Glu Ile
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Glu Ser Leu Ile Pro Lys Glu Ile Ile His Leu Lys Asp Lys Ala Ile
20 25 30

Lys Thr Asn Gln Val Ser Glu Glu Tyr Cys Gln Leu Val Leu Ala Leu
35 40 45

Leu Thr Thr Asn Pro Gly Asn Gln Leu Asn Met Arg Met Thr Lys Val
50 55 60

Lys Ile Asn Gly Ser Pro Val Ser Met Asn Arg Ser Lys Leu Asn Gly
65 70 75 80

His Leu Val Trp Asn Gly Thr Thr Asn Thr Val Asn Ile Leu Thr Lys
85 90 95

Lys Glu Gln Ser Phe Ala Ala Ser Phe Leu Asn Lys Thr Leu Val Lys
100 105 110

Ala Asp Gln Val Lys Gly Tyr Lys Val Leu Ala Glu Asn Ile Phe Ile
115 120 125

Ile Phe Glu Gln Leu Glu Lys Ser Asn Ser Glu Lys Pro Ser Val Tyr
130 135 140

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

Lys Ser Lys Tyr His Glu Glu Ile Lys Tyr Thr Ser Glu Lys Asn Gln
165 170 175

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

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

Cys Lys Glu Met Ser Pro Tyr Leu Asp Tyr Lys Lys Ser Tyr Leu Asn
210 215 220

Arg Lys Lys Glu Ile Leu Ala Asn Ser Ile Gln Gln Asn Arg Gly Phe
225 230 235 240

Ser Met Pro Thr Ala Glu Glu Pro Asn Leu Leu Ser Lys Arg Lys Gln
245 250 255

Leu Phe Gln Gln Trp Ala Met Lys Phe Gln Glu Ser Pro Leu Ile Gln
260 265 270

Gln Asn Asn Phe Ala Val Glu Gln Phe Asn Lys Glu Phe Ala Asn Lys
275 280 285

Ile Asn Glu Leu Ala Ala Val Tyr Asn Val Asp Glu Leu Cys Thr Ala
290 295 300

Ile Thr Glu Lys Leu Met Asn Phe Asp Lys Asp Lys Ser Asn Lys Thr
305 310 315 320

Arg Asn Phe Glu Ile Lys Lys Leu Trp Lys Gln His Pro His Asn Lys
325 330 335

Asp Lys Ala Leu Ile Lys Leu Phe Asn Gln Glu Gly Asn Glu Ala Leu
340 345 350

Asn Gln Phe Asn Ile Glu Leu Gly Lys Tyr Phe Glu His Tyr Phe Pro
355 360 365

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

Thr Ile Ile Lys Thr Val Gly Tyr Gln Leu Arg Asn Ala Phe Val Gln
385 390 395 400

Tyr Leu Leu Gln Val Gly Lys Leu His Gln Tyr Asn Lys Gly Val Leu
405 410 415

Asp Ser Gln Thr Leu Gln Glu Ile Gly Met Tyr Glu Gly Phe Gln Thr
420 425 430

Lys Phe Met Asp Ala Cys Val Phe Ala Ser Ser Ser Leu Arg Asn Ile
435 440 445

Ile Gln Ala Thr Thr Asn Glu Asp Ile Leu Thr Arg Glu Lys Phe Lys
450 455 460

Lys Glu Leu Glu Lys Asn Val Glu Leu Lys His Asp Leu Phe Phe Lys
465 470 475 480

Thr Glu Ile Val Glu Glu Arg Asp Glu Asn Pro Ala Lys Lys Ile Ala
485 490 495

Met Thr Pro Asn Glu Leu Asp Leu Trp Ala Ile Arg Gly Ala Val Gln
500 505 510

Arg Val Arg Asn Gln Ile Phe His Gln Gln Ile Asn Lys Arg His Glu
515 520 525

Pro Asn Gln Leu Lys Val Gly Ser Phe Glu Asn Gly Asp Leu Gly Asn
530 535 540

Val Ser Tyr Gln Lys Thr Ile Tyr Gln Lys Leu Phe Asp Ala Glu Ile
545 550 555 560

Lys Asp Ile Glu Ile Tyr Phe Ala Glu Lys Ile Lys Ser Ser Gly Ala
565 570 575

Leu Glu Gln Tyr Ser Met Lys Asp Leu Glu Lys Leu Phe Ser Asn Lys
580 585 590

Glu Leu Thr Leu Ser Leu Gly Gly Gln Val Val Ala Phe Ala Pro Ser
595 600 605

Tyr Lys Lys Leu Tyr Lys Gln Gly Tyr Phe Tyr Gln Asn Glu Lys Thr
610 615 620

Ile Glu Leu Glu Gln Phe Thr Asp Tyr Asp Phe Ser Asn Asp Val Phe
625 630 635 640

Lys Ala Asn Tyr Tyr Leu Ile Lys Leu Ile Tyr His Tyr Val Phe Leu
645 650 655

Pro Gln Phe Ser Gln Ala Asn Asn Lys Leu Phe Lys Asp Thr Val His
660 665 670

Tyr Val Ile Gln Gln Asn Lys Glu Leu Asn Thr Thr Glu Lys Asp Lys
675 680 685

Lys Asn Asn Lys Lys Ile Arg Lys Tyr Ala Phe Glu Gln Val Lys Leu
690 695 700

Met Lys Asn Glu Ser Pro Glu Lys Tyr Met Gln Tyr Leu Gln Arg Glu
705 710 715 720

Met Gln Glu Glu Arg Thr Ile Lys Glu Ala Lys Lys Thr Asn Glu Glu
725 730 735

Lys Pro Asn Tyr Asn Phe Glu Lys Leu Leu Ile Gln Ile Phe Ile Lys
740 745 750

Gly Phe Asp Thr Phe Leu Arg Asn Phe Asp Leu Asn Leu Asn Pro Ala
755 760 765

Glu Glu Leu Val Gly Thr Val Lys Glu Lys Ala Glu Gly Leu Arg Lys
770 775 780

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

Thr Gly Asp Glu Glu Ile Ala Phe Trp Ile Phe Ala Lys Leu Leu Asp
805 810 815

Ala Arg His Leu Ser Glu Leu Arg Asn Glu Met Ile Lys Phe Lys Gln
820 825 830

Ser Ser Val Lys Lys Gly Leu Ile Lys Asn Gly Asp Leu Ile Glu Gln
835 840 845

Met Gln Pro Ile Leu Glu Leu Cys Ile Leu Ser Asn Asp Ser Glu Ser
850 855 860

Met Glu Lys Glu Ser Phe Asp Lys Ile Glu Val Phe Leu Glu Lys Val
865 870 875 880

Glu Leu Ala Lys Asn Glu Pro Tyr Met Gln Glu Asp Lys Leu Thr Pro
885 890 895

Val Lys Phe Arg Phe Met Lys Gln Leu Glu Lys Tyr Gln Thr Arg Asn
900 905 910

Phe Ile Glu Asn Leu Val Ile Glu Asn Pro Glu Phe Lys Val Ser Glu
915 920 925

Lys Ile Val Leu Asn Trp His Glu Glu Lys Glu Lys Ile Ala Asp Leu
930 935 940

Val Asp Lys Arg Thr Lys Leu His Glu Glu Trp Ala Ser Lys Ala Arg
945 950 955 960

Glu Ile Glu Glu Tyr Asn Glu Lys Ile Lys Lys Asn Lys Ser Lys Lys
965 970 975

Leu Asp Lys Pro Ala Glu Phe Ala Lys Phe Ala Glu Tyr Lys Ile Ile
980 985 990

Cys Glu Ala Ile Glu Asn Phe Asn Arg Leu Asp His Lys Val Arg Leu
995 1000 1005

Thr Tyr Leu Lys Asn Leu His Tyr Leu Met Ile Asp Leu Met Gly
1010 1015 1020

Arg Met Val Gly Phe Ser Val Leu Phe Glu Arg Asp Phe Val Tyr
1025 1030 1035

Met Gly Arg Ser Tyr Ser Ala Leu Lys Lys Gln Ser Ile Tyr Leu
1040 1045 1050

Asn Asp Tyr Asp Thr Phe Ala Asn Ile Arg Asp Trp Glu Val Asn
1055 1060 1065

Glu Asn Lys His Leu Phe Gly Thr Ser Ser Ser Asp Leu Thr Phe
1070 1075 1080

Gln Glu Thr Ala Glu Phe Lys Asn Leu Lys Lys Pro Met Glu Asn
1085 1090 1095

Gln Leu Lys Ala Leu Leu Gly Val Thr Asn His Ser Phe Glu Ile
1100 1105 1110

Arg Asn Asn Ile Ala His Leu His Val Leu Arg Asn Asp Gly Lys
1115 1120 1125

Gly Glu Gly Val Ser Leu Leu Ser Cys Met Asn Asp Leu Arg Lys
1130 1135 1140

Leu Met Ser Tyr Asp Arg Lys Leu Lys Asn Ala Val Thr Lys Ala
1145 1150 1155

Ile Ile Lys Ile Leu Asp Lys His Gly Met Ile Leu Lys Leu Thr
1160 1165 1170

Asn Asn Asp His Thr Lys Pro Phe Glu Ile Glu Ser Leu Lys Pro
1175 1180 1185

Lys Lys Ile Ile His Leu Glu Lys Ser Asn His Ser Phe Pro Met
1190 1195 1200

Asp Gln Val Ser Gln Glu Tyr Cys Asp Leu Val Lys Lys Met Leu
1205 1210 1215

Val Phe Thr Asn
1220

<210> 40

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Cga2Cas13a direct repeat

<400> 40

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36

<210> 41

<211> 3465

<212> DNA

<213> Artificial Sequence

<220>

<223> PprCas13a nucleic acid sequence

<400> 41

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aacatcctgc ctgagaagaa gaggcagtcc tttagacctgt ctaccctgaa caagacaatc 180

atcaagttcg acacagccaa gaagcagaag ctgaatgtgg atcagtacaa gatcgtggag 240

aagatcttta agtatcctaa gcaggagctg ccaaagcaga tcaaggccga ggagatcctg 300

ccatttctga atcacaagtt ccaggagccc gtgaagtact ggaagaacgg caaggaggag 360

tccttcaatc tgaccctgct gatcgtggag gccgtgcagg cacaggacaa gcgcaagctg 420

cagccctact atgattggaa aacctggtat atccagacaa agagcgacct gctgaagaag 480

tccatcgaga acaataggat cgatctgaca gagaacctgt ctaagcgcaa gaaggccctg 540

ctggcctggg agacagagtt cacagccagc ggctccatcg acctgaccca ctaccacaag 600

gtgtatatga cagacgtgct gtgcaagatg ctgcaggatg tgaagccact gaccgacgat 660

aagggaaga tcaacacaaa tgcctaccac cggggcctga agaaggccct gcagaatcac 720

cagcctgcca tctttggcac ccgggaggtg ccaaagcagg ccaatagagc cgataaccag 780

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ctgctgaagg acaacacaaa tagccagctg tactccttct ttttcggcga gggcctgagc 1200

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aactactata acaatgcctt cctgcacgtg agcaatgacg agatcaagga gaagcagatg	3120
tacgatatca gaaaccacat cgcccacttt aattatctga ccaaggacgc cgccgatttc	3180
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aatgccgtgt ccaaggcctt tatcgacctg ttcgataagc acggcatgat cctgaagctg	3300
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ctgggctcct ctgccaagga taagccagag taccagtatt gtaccaacca ggtcatgatg	3420
gcctattgca atatgtgccg gagcctgctg gagatgaaga agtga	3465

<210> 42
 <211> 1154
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PprCas13a amino acid sequence

 <400> 42

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Gln Pro Val Ser	Asn Glu Thr Ser	Asn Ile Leu Pro	Glu Lys Lys Arg
	35	40	45
Gln Ser Phe Asp	Leu Ser Thr Leu	Asn Lys Thr Ile	Ile Lys Phe Asp
	50	55	60
Thr Ala Lys Lys	Gln Lys Leu Asn	Val Asp Gln Tyr	Lys Ile Val Glu
65	70	75	80

Lys Ile Phe Lys Tyr Pro Lys Gln Glu Leu Pro Lys Gln Ile Lys Ala
85 90 95

Glu Glu Ile Leu Pro Phe Leu Asn His Lys Phe Gln Glu Pro Val Lys
100 105 110

Tyr Trp Lys Asn Gly Lys Glu Glu Ser Phe Asn Leu Thr Leu Leu Ile
115 120 125

Val Glu Ala Val Gln Ala Gln Asp Lys Arg Lys Leu Gln Pro Tyr Tyr
130 135 140

Asp Trp Lys Thr Trp Tyr Ile Gln Thr Lys Ser Asp Leu Leu Lys Lys
145 150 155 160

Ser Ile Glu Asn Asn Arg Ile Asp Leu Thr Glu Asn Leu Ser Lys Arg
165 170 175

Lys Lys Ala Leu Leu Ala Trp Glu Thr Glu Phe Thr Ala Ser Gly Ser
180 185 190

Ile Asp Leu Thr His Tyr His Lys Val Tyr Met Thr Asp Val Leu Cys
195 200 205

Lys Met Leu Gln Asp Val Lys Pro Leu Thr Asp Asp Lys Gly Lys Ile
210 215 220

Asn Thr Asn Ala Tyr His Arg Gly Leu Lys Lys Ala Leu Gln Asn His
225 230 235 240

Gln Pro Ala Ile Phe Gly Thr Arg Glu Val Pro Asn Glu Ala Asn Arg
245 250 255

Ala Asp Asn Gln Leu Ser Ile Tyr His Leu Glu Val Val Lys Tyr Leu
260 265 270

Glu His Tyr Phe Pro Ile Lys Thr Ser Lys Arg Arg Asn Thr Ala Asp
275 280 285

Asp Ile Ala His Tyr Leu Lys Ala Gln Thr Leu Lys Thr Thr Ile Glu
290 295 300

Lys Gln Leu Val Asn Ala Ile Arg Ala Asn Ile Ile Gln Gln Gly Lys
305 310 315 320

Thr Asn His His Glu Leu Lys Ala Asp Thr Thr Ser Asn Asp Leu Ile
325 330 335

Arg Ile Lys Thr Asn Glu Ala Phe Val Leu Asn Leu Thr Gly Thr Cys
340 345 350

Ala Phe Ala Ala Asn Asn Ile Arg Asn Met Val Asp Asn Glu Gln Thr
355 360 365

Asn Asp Ile Leu Gly Lys Gly Asp Phe Ile Lys Ser Leu Leu Lys Asp
370 375 380

Asn Thr Asn Ser Gln Leu Tyr Ser Phe Phe Phe Gly Glu Gly Leu Ser
385 390 395 400

Thr Asn Lys Ala Glu Lys Glu Thr Gln Leu Trp Gly Ile Arg Gly Ala
405 410 415

Val Gln Gln Ile Arg Asn Asn Val Asn His Tyr Lys Lys Asp Ala Leu
420 425 430

Lys Thr Val Phe Asn Ile Ser Asn Phe Glu Asn Pro Thr Ile Thr Asp
435 440 445

Pro Lys Gln Gln Thr Asn Tyr Ala Asp Thr Ile Tyr Lys Ala Arg Phe
450 455 460

Ile Asn Glu Leu Glu Lys Ile Pro Glu Ala Phe Ala Gln Gln Leu Lys
465 470 475 480

Thr Gly Gly Ala Val Ser Tyr Tyr Thr Ile Glu Asn Leu Lys Ser Leu
485 490 495

Leu Thr Thr Phe Gln Phe Ser Leu Cys Arg Ser Thr Ile Pro Phe Ala
500 505 510

Pro Gly Phe Lys Lys Val Phe Asn Gly Gly Ile Asn Tyr Gln Asn Ala
515 520 525

Lys Gln Asp Glu Ser Phe Tyr Glu Leu Met Leu Glu Gln Tyr Leu Arg
530 535 540

Lys Glu Asn Phe Ala Glu Glu Ser Tyr Asn Ala Arg Tyr Phe Met Leu
545 550 555 560

Lys Leu Ile Tyr Asn Asn Leu Phe Leu Pro Gly Phe Thr Thr Asp Arg
565 570 575

Lys Ala Phe Ala Asp Ser Val Gly Phe Val Gln Met Gln Asn Lys Lys
580 585 590

Gln Ala Glu Lys Val Asn Pro Arg Lys Lys Glu Ala Tyr Ala Phe Glu
595 600 605

Ala Val Arg Pro Met Thr Ala Ala Asp Ser Ile Ala Asp Tyr Met Ala
610 615 620

Tyr Val Gln Ser Glu Leu Met Gln Glu Gln Asn Lys Lys Glu Glu Lys
625 630 635 640

Val Ala Glu Glu Thr Arg Ile Asn Phe Glu Lys Phe Val Leu Gln Val
645 650 655

Phe Ile Lys Gly Phe Asp Ser Phe Leu Arg Ala Lys Glu Phe Asp Phe
660 665 670

Val Gln Met Pro Gln Pro Gln Leu Thr Ala Thr Ala Ser Asn Gln Gln
675 680 685

Lys Ala Asp Lys Leu Asn Gln Leu Glu Ala Ser Ile Thr Ala Asp Cys
690 695 700

Lys Leu Thr Pro Gln Tyr Ala Lys Ala Asp Asp Ala Thr His Ile Ala
705 710 715 720

Phe Tyr Val Phe Cys Lys Leu Leu Asp Ala Ala His Leu Ser Asn Leu
725 730 735

Arg Asn Glu Leu Ile Lys Phe Arg Glu Ser Val Asn Glu Phe Lys Phe
740 745 750

His His Leu Leu Glu Ile Ile Glu Ile Cys Leu Leu Ser Ala Asp Val
755 760 765

Val Pro Thr Asp Tyr Arg Asp Leu Tyr Ser Ser Glu Ala Asp Cys Leu
770 775 780

Ala Arg Leu Arg Pro Phe Ile Glu Gln Gly Ala Asp Ile Thr Asn Trp
785 790 795 800

Ser Asp Leu Phe Val Gln Ser Asp Lys His Ser Pro Val Ile His Ala
805 810 815

Asn Ile Glu Leu Ser Val Lys Tyr Gly Thr Thr Lys Leu Leu Glu Gln
820 825 830

Ile Ile Asn Lys Asp Thr Gln Phe Lys Thr Thr Glu Ala Asn Phe Thr
835 840 845

Ala Trp Asn Thr Ala Gln Lys Ser Ile Glu Gln Leu Ile Lys Gln Arg
850 855 860

Glu Asp His His Glu Gln Trp Val Lys Ala Lys Asn Ala Asp Asp Lys
865 870 875 880

Glu Lys Gln Glu Arg Lys Arg Glu Lys Ser Asn Phe Ala Gln Lys Phe
885 890 895

Ile Glu Lys His Gly Asp Asp Tyr Leu Asp Ile Cys Asp Tyr Ile Asn
900 905 910

Thr Tyr Asn Trp Leu Asp Asn Lys Met His Phe Val His Leu Asn Arg
915 920 925

Leu His Gly Leu Thr Ile Glu Leu Leu Gly Arg Met Ala Gly Phe Val
930 935 940

Ala Leu Phe Asp Arg Asp Phe Gln Phe Phe Asp Glu Gln Gln Ile Ala
945 950 955 960

Asp Glu Phe Lys Leu His Gly Phe Val Asn Leu His Ser Ile Asp Lys
965 970 975

Lys Leu Asn Glu Val Pro Thr Lys Lys Ile Lys Glu Ile Tyr Asp Ile
980 985 990

Arg Asn Lys Ile Ile Gln Ile Asn Gly Asn Lys Ile Asn Glu Ser Val
995 1000 1005

Arg Ala Asn Leu Ile Gln Phe Ile Ser Ser Lys Arg Asn Tyr Tyr
1010 1015 1020

Asn Asn Ala Phe Leu His Val Ser Asn Asp Glu Ile Lys Glu Lys
1025 1030 1035

Gln Met Tyr Asp Ile Arg Asn His Ile Ala His Phe Asn Tyr Leu
1040 1045 1050

Thr Lys Asp Ala Ala Asp Phe Ser Leu Ile Asp Leu Ile Asn Glu
1055 1060 1065

Leu Arg Glu Leu Leu His Tyr Asp Arg Lys Leu Lys Asn Ala Val
1070 1075 1080

Ser Lys Ala Phe Ile Asp Leu Phe Asp Lys His Gly Met Ile Leu
1085 1090 1095

Lys Leu Lys Leu Asn Ala Asp His Lys Leu Lys Val Glu Ser Leu
1100 1105 1110

Glu Pro Lys Lys Ile Tyr His Leu Gly Ser Ser Ala Lys Asp Lys
1115 1120 1125

Pro Glu Tyr Gln Tyr Cys Thr Asn Gln Val Met Met Ala Tyr Cys
1130 1135 1140

Asn Met Cys Arg Ser Leu Leu Glu Met Lys Lys
1145 1150

<210> 43
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> PprCas13a direct repeat

<400> 43
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<210> 44
<211> 2913
<212> DNA
<213> Artificial Sequence

<220>
<223> LweCas13a nucleic acid sequence

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ccttccaagg gagcagagca cgtgcagttc tgcctgaccg acatcgccgt gcccgaatc 180
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gcctttctga atggagagcc actgggcctg gacctggtgg ccaagaagta caagctggcc 420
gatctggccg agtccttcaa ggtggtggac ctgaacgagg ataagtctgc caattataag 480
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gactccaccg aggatacacc aaaccacttt gagaagttca tctctcaggt gtttatcaag	1680
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ctgggcgaga agaagatcga taacggctac atcgagacaa atcaggtgag cgaggagtat      2880
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<210> 45
<211> 970
<212> PRT
<213> Artificial Sequence

<220>
<223> LweCas13a amino acid sequence

<400> 45

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Met Leu Ala Leu Leu His Gln Glu Val Pro Ser Gln Lys Leu His Asn
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Leu Lys Ser Leu Asn Thr Glu Ser Leu Thr Lys Leu Phe Lys Pro Lys
20           25           30

```

```

Phe Gln Asn Met Ile Ser Tyr Pro Pro Ser Lys Gly Ala Glu His Val
35           40           45

```

```

Gln Phe Cys Leu Thr Asp Ile Ala Val Pro Ala Ile Arg Asp Leu Asp
50           55           60

```

```

Glu Ile Lys Pro Asp Trp Gly Ile Phe Phe Glu Lys Leu Lys Pro Tyr
65           70           75           80

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```

Thr Asp Trp Ala Glu Ser Tyr Ile His Tyr Lys Gln Thr Thr Ile Gln
85           90           95

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Lys Ser Ile Glu Gln Asn Lys Ile Gln Ser Pro Asp Ser Pro Arg Lys
100          105          110

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

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Gly Leu Asp Leu Val Ala Lys Lys Tyr Lys Leu Ala Asp Leu Ala Glu
130 135 140

Ser Phe Lys Val Val Asp Leu Asn Glu Asp Lys Ser Ala Asn Tyr Lys
145 150 155 160

Ile Lys Ala Cys Leu Gln Gln His Gln Arg Asn Ile Leu Asp Glu Leu
165 170 175

Lys Glu Asp Pro Glu Leu Asn Gln Tyr Gly Ile Glu Val Lys Lys Tyr
180 185 190

Ile Gln Arg Tyr Phe Pro Ile Lys Arg Ala Pro Asn Arg Ser Lys His
195 200 205

Ala Arg Ala Asp Phe Leu Lys Lys Glu Leu Ile Glu Ser Thr Val Glu
210 215 220

Gln Gln Phe Lys Asn Ala Val Tyr His Tyr Val Leu Glu Gln Gly Lys
225 230 235 240

Met Glu Ala Tyr Glu Leu Thr Asp Pro Lys Thr Lys Asp Leu Gln Asp
245 250 255

Ile Arg Ser Gly Glu Ala Phe Ser Phe Lys Phe Ile Asn Ala Cys Ala
260 265 270

Phe Ala Ser Asn Asn Leu Lys Met Ile Leu Asn Pro Glu Cys Glu Lys
275 280 285

Asp Ile Leu Gly Lys Gly Asp Phe Lys Lys Asn Leu Pro Asn Ser Thr
290 295 300

Thr Gln Ser Asp Val Val Lys Lys Met Ile Pro Phe Phe Ser Asp Glu
305 310 315 320

Ile Gln Asn Val Asn Phe Asp Glu Ala Ile Trp Ala Ile Arg Gly Ser
325 330 335

Ile Gln Gln Ile Arg Asn Glu Val Tyr His Cys Lys Lys His Ser Trp
340 345 350

Lys Ser Ile Leu Lys Ile Lys Gly Phe Glu Phe Glu Pro Asn Asn Met
355 360 365

Lys Tyr Thr Asp Ser Asp Met Gln Lys Leu Met Asp Lys Asp Ile Ala
370 375 380

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

Arg Phe Tyr Ser His Asp Lys Leu Gln Ser Ile Trp Glu Met Lys Gln
405 410 415

Gly Phe Ser Leu Leu Thr Thr Asn Ala Pro Phe Val Pro Ser Phe Lys
420 425 430

Arg Val Tyr Ala Lys Gly His Asp Tyr Gln Thr Ser Lys Asn Arg Tyr
435 440 445

Tyr Asp Leu Gly Leu Thr Thr Phe Asp Ile Leu Glu Tyr Gly Glu Glu
450 455 460

Asp Phe Arg Ala Arg Tyr Phe Leu Thr Lys Leu Val Tyr Tyr Gln Gln
465 470 475 480

Phe Met Pro Trp Phe Thr Ala Asp Asn Asn Ala Phe Arg Asp Ala Ala
485 490 495

Asn Phe Val Leu Arg Leu Asn Lys Asn Arg Gln Gln Asp Ala Lys Ala
500 505 510

Phe Ile Asn Ile Arg Glu Val Glu Glu Gly Glu Met Pro Arg Asp Tyr
515 520 525

Met Gly Tyr Val Gln Gly Gln Ile Ala Ile His Glu Asp Ser Thr Glu
530 535 540

Asp Thr Pro Asn His Phe Glu Lys Phe Ile Ser Gln Val Phe Ile Lys
545 550 555 560

Gly Phe Asp Ser His Met Arg Ser Ala Asp Leu Lys Phe Ile Lys Asn
565 570 575

Pro Arg Asn Gln Gly Leu Glu Gln Ser Glu Ile Glu Glu Met Ser Phe
580 585 590

Asp Ile Lys Val Glu Pro Ser Phe Leu Lys Asn Lys Asp Asp Tyr Ile
595 600 605

Ala Phe Trp Thr Phe Cys Lys Met Leu Asp Ala Arg His Leu Ser Glu
610 615 620

Leu Arg Asn Glu Met Ile Lys Tyr Asp Gly His Leu Thr Gly Glu Gln
625 630 635 640

Glu Ile Ile Gly Leu Ala Leu Leu Gly Val Asp Ser Arg Glu Asn Asp
645 650 655

Trp Lys Gln Phe Phe Ser Ser Glu Arg Glu Tyr Glu Lys Ile Met Lys
660 665 670

Gly Tyr Val Gly Glu Glu Leu Tyr Gln Arg Glu Pro Tyr Arg Gln Ser
675 680 685

Asp Gly Lys Thr Pro Ile Leu Phe Arg Gly Val Glu Gln Ala Arg Lys
690 695 700

Tyr Gly Thr Glu Thr Val Ile Gln Arg Leu Phe Asp Ala Ser Pro Glu
705 710 715 720

Phe Lys Val Ser Lys Cys Asn Ile Thr Glu Trp Glu Arg Gln Lys Glu
725 730 735

Thr Ile Glu Glu Thr Ile Glu Arg Arg Lys Glu Leu His Asn Glu Trp
740 745 750

Glu Lys Asn Pro Lys Lys Pro Gln Asn Asn Ala Phe Phe Lys Glu Tyr
755 760 765

Lys Glu Cys Cys Asp Ala Ile Asp Ala Tyr Asn Trp His Lys Asn Lys
770 775 780

Thr Thr Leu Val Tyr Val Asn Glu Leu His His Leu Leu Ile Glu Ile
785 790 795 800

Leu Gly Arg Tyr Val Gly Tyr Val Ala Ile Ala Asp Arg Asp Phe Gln
805 810 815

Cys Met Ala Asn Gln Tyr Phe Lys His Ser Gly Ile Thr Glu Arg Val
820 825 830

Glu Tyr Trp Gly Asp Asn Arg Leu Lys Ser Ile Lys Lys Leu Asp Thr
835 840 845

Phe Leu Lys Lys Glu Gly Leu Phe Val Ser Glu Lys Asn Ala Arg Asn
850 855 860

His Ile Ala His Leu Asn Tyr Leu Ser Leu Lys Ser Glu Cys Thr Leu
865 870 875 880

Leu Tyr Leu Ser Glu Arg Leu Arg Glu Ile Phe Lys Tyr Asp Arg Lys
885 890 895

Leu Lys Asn Ala Val Ser Lys Ser Leu Ile Asp Ile Leu Asp Arg His
900 905 910

Gly Met Ser Val Val Phe Ala Asn Leu Lys Glu Asn Lys His Arg Leu
915 920 925

Val Ile Lys Ser Leu Glu Pro Lys Lys Leu Arg His Leu Gly Glu Lys
930 935 940

Lys Ile Asp Asn Gly Tyr Ile Glu Thr Asn Gln Val Ser Glu Glu Tyr
945 950 955 960

Cys Gly Ile Val Lys Arg Leu Leu Glu Ile
965 970

<210> 46

<211> 36

<212> DNA
<213> Artificial Sequence

<220>
<223> LweCas13a direct repeat

<400> 46
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<210> 47
<211> 3156
<212> DNA
<213> Artificial Sequence

<220>
<223> LbfCas13a nucleic acid sequence

<400> 47
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aagaagaagg agagcttcta caagtccatc ctgaacaaga ccgtgagaaa gcctgatgag 180
aaggagaaga atcggagaaa gcaggccatc aacaaggcca tcaataagga gatcacagag 240
ctgatgctgg ccgtgctgca ccaggaggtg cctagccaga agctgcacaa cctgaagagc 300
ctgaataaccg agtccctgac aaagctgttt aagccaaagt tccagaatat gatctcttat 360
ccacctagca agggagcaga gcacgtgcag ttctgcctga ccgacatcgc cgtgcccgc 420
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tacacagatt gggccgagtc ctacatccac tataagcaga ccacaatcca gaagtctatc 540
gagcagaaca agatccagag cccagactcc cccagaaagc tgggtgctgca gaagtatgtg 600
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<210> 48
 <211> 1050
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> LbfCas13a amino acid sequence

<400> 48

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Arg	Thr	Ser	Lys	Glu	Gly	Gln	Leu	Gly	Tyr	Glu	Gly	Ile	Asp	Gly	Asn
			20					25					30		

Lys	Thr	Thr	Glu	Ile	Ile	Phe	Asp	Lys	Lys	Lys	Glu	Ser	Phe	Tyr	Lys
			35				40					45			

Ser	Ile	Leu	Asn	Lys	Thr	Val	Arg	Lys	Pro	Asp	Glu	Lys	Glu	Lys	Asn
	50					55					60				

Arg	Arg	Lys	Gln	Ala	Ile	Asn	Lys	Ala	Ile	Asn	Lys	Glu	Ile	Thr	Glu
65					70				75						80

Leu	Met	Leu	Ala	Val	Leu	His	Gln	Glu	Val	Pro	Ser	Gln	Lys	Leu	His
			85					90						95	

Asn	Leu	Lys	Ser	Leu	Asn	Thr	Glu	Ser	Leu	Thr	Lys	Leu	Phe	Lys	Pro
			100					105					110		

Lys Phe Gln Asn Met Ile Ser Tyr Pro Pro Ser Lys Gly Ala Glu His
115 120 125

Val Gln Phe Cys Leu Thr Asp Ile Ala Val Pro Ala Ile Arg Asp Leu
130 135 140

Asp Glu Ile Lys Pro Asp Trp Gly Ile Phe Phe Glu Lys Leu Lys Pro
145 150 155 160

Tyr Thr Asp Trp Ala Glu Ser Tyr Ile His Tyr Lys Gln Thr Thr Ile
165 170 175

Gln Lys Ser Ile Glu Gln Asn Lys Ile Gln Ser Pro Asp Ser Pro Arg
180 185 190

Lys Leu Val Leu Gln Lys Tyr Val Thr Ala Phe Leu Asn Gly Glu Pro
195 200 205

Leu Gly Leu Asp Leu Val Ala Lys Lys Tyr Lys Leu Ala Asp Leu Ala
210 215 220

Glu Ser Phe Lys Leu Val Asp Leu Asn Glu Asp Lys Ser Ala Asn Tyr
225 230 235 240

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

Leu Lys Glu Asp Pro Glu Leu Asn Gln Tyr Gly Ile Glu Val Lys Lys
260 265 270

Tyr Ile Gln Arg Tyr Phe Pro Ile Lys Arg Ala Pro Asn Arg Ser Lys
275 280 285

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

Glu Gln Gln Phe Lys Asn Ala Val Tyr His Tyr Val Leu Glu Gln Gly
305 310 315 320

Lys Met Glu Ala Tyr Glu Leu Thr Asp Pro Lys Thr Lys Asp Leu Gln
325 330 335

Asp Ile Arg Ser Gly Glu Ala Phe Ser Phe Lys Phe Ile Asn Ala Cys
340 345 350

Ala Phe Ala Ser Asn Asn Leu Lys Met Ile Leu Asn Pro Glu Cys Glu
355 360 365

Lys Asp Ile Leu Gly Lys Gly Asn Phe Lys Lys Asn Leu Pro Asn Ser
370 375 380

Thr Thr Arg Ser Asp Val Val Lys Lys Met Ile Pro Phe Phe Ser Asp
385 390 395 400

Glu Leu Gln Asn Val Asn Phe Asp Glu Ala Ile Trp Ala Ile Arg Gly
405 410 415

Ser Ile Gln Gln Ile Arg Asn Glu Val Tyr His Cys Lys Lys His Ser
420 425 430

Trp Lys Ser Ile Leu Lys Ile Lys Gly Phe Glu Phe Glu Pro Asn Asn
435 440 445

Met Lys Tyr Ala Asp Ser Asp Met Gln Lys Leu Met Asp Lys Asp Ile
450 455 460

Ala Lys Ile Pro Glu Phe Ile Glu Glu Lys Leu Lys Ser Ser Gly Val
465 470 475 480

Val Arg Phe Tyr Arg His Asp Glu Leu Gln Ser Ile Trp Glu Met Lys
485 490 495

Gln Gly Phe Ser Leu Leu Thr Thr Asn Ala Pro Phe Val Pro Ser Phe
500 505 510

Lys Arg Val Tyr Ala Lys Gly His Asp Tyr Gln Thr Ser Lys Asn Arg
515 520 525

Tyr Tyr Asn Leu Asp Leu Thr Thr Phe Asp Ile Leu Glu Tyr Gly Glu
530 535 540

Glu Asp Phe Arg Ala Arg Tyr Phe Leu Thr Lys Leu Val Tyr Tyr Gln
545 550 555 560

Gln Phe Met Pro Trp Phe Thr Ala Asp Asn Asn Ala Phe Arg Asp Ala
565 570 575

Ala Asn Phe Val Leu Arg Leu Asn Lys Asn Arg Gln Gln Asp Ala Lys
580 585 590

Ala Phe Ile Asn Ile Arg Glu Val Glu Glu Gly Glu Met Pro Arg Asp
595 600 605

Tyr Met Gly Tyr Val Gln Gly Gln Ile Ala Ile His Glu Asp Ser Ile
610 615 620

Glu Asp Thr Pro Asn His Phe Glu Lys Phe Ile Ser Gln Val Phe Ile
625 630 635 640

Lys Gly Phe Asp Arg His Met Arg Ser Ala Asn Leu Lys Phe Ile Lys
645 650 655

Asn Pro Arg Asn Gln Gly Leu Glu Gln Ser Glu Ile Glu Glu Met Ser
660 665 670

Phe Asp Ile Lys Val Glu Pro Ser Phe Leu Lys Asn Lys Asp Asp Tyr
675 680 685

Ile Ala Phe Trp Ile Phe Cys Lys Met Leu Asp Ala Arg His Leu Ser
690 695 700

Glu Leu Arg Asn Glu Met Ile Lys Tyr Asp Gly His Leu Thr Gly Glu
705 710 715 720

Gln Glu Ile Ile Gly Leu Leu Leu Gly Val Asp Ser Arg Glu Asn Asp
725 730 735

Trp Lys Gln Phe Phe Ser Ser Glu Arg Glu Tyr Glu Lys Ile Met Lys
740 745 750

Gly Tyr Val Val Glu Glu Leu Tyr Gln Arg Glu Pro Tyr Arg Gln Ser
755 760 765

Asp Gly Lys Thr Pro Ile Leu Phe Arg Gly Val Glu Gln Ala Arg Lys
770 775 780

Tyr Gly Thr Glu Thr Val Ile Gln Arg Leu Phe Asp Ala Asn Pro Glu
785 790 795 800

Phe Lys Val Ser Lys Cys Asn Leu Ala Glu Trp Glu Arg Gln Lys Glu
805 810 815

Thr Ile Glu Glu Thr Ile Lys Arg Arg Lys Glu Leu His Asn Glu Trp
820 825 830

Ala Lys Asn Pro Lys Lys Pro Gln Asn Asn Ala Phe Phe Lys Glu Tyr
835 840 845

Lys Glu Cys Cys Asp Ala Ile Asp Ala Tyr Asn Trp His Lys Asn Lys
850 855 860

Thr Thr Leu Ala Tyr Val Asn Glu Leu His His Leu Leu Ile Glu Ile
865 870 875 880

Leu Gly Arg Tyr Val Gly Tyr Val Ala Ile Ala Asp Arg Asp Phe Gln
885 890 895

Cys Met Ala Asn Gln Tyr Phe Lys His Ser Gly Ile Thr Glu Arg Val
900 905 910

Glu Tyr Trp Gly Asp Asn Arg Leu Lys Ser Ile Lys Lys Leu Asp Thr
915 920 925

Phe Leu Lys Lys Glu Gly Leu Phe Val Ser Glu Lys Asn Ala Arg Asn
930 935 940

His Ile Ala His Leu Asn Tyr Leu Ser Leu Lys Ser Glu Cys Thr Leu
945 950 955 960

Leu Tyr Leu Ser Glu Arg Leu Arg Glu Ile Phe Lys Tyr Asp Arg Lys
965 970 975

Leu Lys Asn Ala Val Ser Lys Ser Leu Ile Asp Ile Leu Asp Arg His
980 985 990

Gly Met Ser Val Val Phe Ala Asn Leu Lys Glu Asn Lys His Arg Leu
995 1000 1005

Val Ile Lys Ser Leu Glu Pro Lys Lys Leu Arg His Leu Gly Gly
1010 1015 1020

Lys Lys Ile Asp Gly Gly Tyr Ile Glu Thr Asn Gln Val Ser Glu
1025 1030 1035

Glu Tyr Cys Gly Ile Val Lys Arg Leu Leu Glu Met
1040 1045 1050

<210> 49
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> LbfCas13a direct repeat

<400> 49
gatttagagt acctcaaaac aaaagaggac taaaac 36

<210> 50
<211> 3459
<212> DNA
<213> Artificial Sequence

<220>
<223> Lwa2Cas13a nucleic acid sequence

<400> 50
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aggctggaca tctacatcaa gaaccccgat aatgcctccg aggaggagaa ccgcatccgg 180
agagagaatc tgaagaagtt cttttctaac aaggtgctgc acctgaagga cagcgtgctg 240
tacctgaaga acaggaagga gaagaatgcc gtgcaggata agaattattc cgaggaggac 300
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aacgaggacg tgaatagcga ggagctggag atcttcagga aggatgtgga ggccaagctg	420
aacaagatca attctctgaa gtatagcttt gaggagaaca aggccaatta ccagaagatc	480
aacgagaaca atgtggagaa agtgggcggc aagagcaagc gcaacatcat ctatgactac	540
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ctgtataaga aggaggatat cgagaagctg ttctttctga tcgagaactc caagaagcac	660
gagaagtaca agatccggga gtactatcac aagatcatcg gcagaaagaa cgacaaggag	720
aatttcgcca agatcatcta tgaggagatc cagaacgtga acaatatcaa ggagctgac	780
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gagatgagcc agctgctgaa gaactacgtg tataagcggc tgtctaacat cagcaatgac	960
aagatcaaga gaatcttcga gtaccagaat ctgaagaagc tgatcgagaa caagctgctg	1020
aataagctgg acacctatgt gcgcaactgt ggcaagtaca attactatct gcaagtgggc	1080
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gacaaggagg agaaggatgc ccagatctac ctgctgaaga acatctacta tggcgagttc	1800
ctgaacaagt ttgtgaagaa cagcaagggtg ttctttaaga tcacaaatga agtgatcaag	1860
atcaacaagc agcggaatca gaaaaccggc cactacaagt atcagaagtt cgagaacatc	1920
gagaaaaccg tgcccgtgga gtacctggcc atcatccaga gcagagagat gatcaacaat	1980

caggacaagg aggagaagaa cacctatatc gattttcatcc agcagatctt cctgaagggc	2040
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aacaacgata tcttttctaa gatcaagatc aagaaggaca acaaggagaa gtatgataag	2160
atcctgaaga attacgagaa gcacaacagg aataaggaga tccccacga gatcaacgag	2220
ttcgtgcgcg agatcaagct gggcaagatc ctgaagtata cagagaacct gaatatgttt	2280
tacctgatcc tgaagctgct gaaccacaag gagctgacca atctgaaggg ctctctggag	2340
aagtaccaga gcgccaacaa ggaggagaca ttcagcgatg agctggagct gatcaatctg	2400
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aataaggtgg agtttaatga gctgaacctg ctgcagggcc tgctgctgaa gatcctgcac	2880
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aatgtggaga agcggagcat ctactccgat aagaaggtga agaagctgaa gcaggagaag	3120
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agcctgctgg aggtgctgga gaacctgagg aagctgctgt cttacgaccg caagctgaag	3240
aatgccatca tgaagagcat cgtggatatc ctgaaggagt atggcttcgt ggccaccttc	3300
aagatcggcg ccgacaagaa gatcgagatc cagaccctgg agagcgagaa gatcgtgcac	3360
ctgaagaacc tgaagaagaa gaagctgatg acagatcgga acagcgagga gctgtgagag	3420
ctggtgaaag tgatgttcga gtacaaggcc ctggagtga	3459

<210> 51

<211> 1152

<212> PRT
<213> Artificial Sequence

<220>
<223> Lwa2Cas13a amino acid sequence

<400> 51

Met Lys Val Thr Lys Val Asp Gly Ile Ser His Lys Lys Tyr Ile Glu
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Glu Gly Lys Leu Val Lys Ser Thr Ser Glu Glu Asn Arg Thr Ser Glu
20 25 30

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

Pro Asp Asn Ala Ser Glu Glu Glu Asn Arg Ile Arg Arg Glu Asn Leu
50 55 60

Lys Lys Phe Phe Ser Asn Lys Val Leu His Leu Lys Asp Ser Val Leu
65 70 75 80

Tyr Leu Lys Asn Arg Lys Glu Lys Asn Ala Val Gln Asp Lys Asn Tyr
85 90 95

Ser Glu Glu Asp Ile Ser Glu Tyr Asp Leu Lys Asn Lys Asn Ser Phe
100 105 110

Ser Val Leu Lys Lys Ile Leu Leu Asn Glu Asp Val Asn Ser Glu Glu
115 120 125

Leu Glu Ile Phe Arg Lys Asp Val Glu Ala Lys Leu Asn Lys Ile Asn
130 135 140

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

Asn Glu Asn Asn Val Glu Lys Val Gly Gly Lys Ser Lys Arg Asn Ile
165 170 175

Ile Tyr Asp Tyr Tyr Arg Glu Ser Ala Lys Arg Asn Asp Tyr Ile Asn
180 185 190

Asn Val Gln Glu Ala Phe Asp Lys Leu Tyr Lys Lys Glu Asp Ile Glu
195 200 205

Lys Leu Phe Phe Leu Ile Glu Asn Ser Lys Lys His Glu Lys Tyr Lys
210 215 220

Ile Arg Glu Tyr Tyr His Lys Ile Ile Gly Arg Lys Asn Asp Lys Glu
225 230 235 240

Asn Phe Ala Lys Ile Ile Tyr Glu Glu Ile Gln Asn Val Asn Asn Ile
245 250 255

Lys Glu Leu Ile Glu Lys Ile Pro Asp Met Ser Glu Leu Lys Lys Ser
260 265 270

Gln Val Phe Tyr Lys Tyr Tyr Leu Asp Lys Glu Glu Leu Asn Asp Lys
275 280 285

Asn Ile Lys Tyr Ala Phe Cys His Phe Val Glu Ile Glu Met Ser Gln
290 295 300

Leu Leu Lys Asn Tyr Val Tyr Lys Arg Leu Ser Asn Ile Ser Asn Asp
305 310 315 320

Lys Ile Lys Arg Ile Phe Glu Tyr Gln Asn Leu Lys Lys Leu Ile Glu
325 330 335

Asn Lys Leu Leu Asn Lys Leu Asp Thr Tyr Val Arg Asn Cys Gly Lys
340 345 350

Tyr Asn Tyr Tyr Leu Gln Val Gly Glu Ile Ala Thr Ser Asp Phe Ile
355 360 365

Ala Arg Asn Arg Gln Asn Glu Ala Phe Leu Arg Asn Ile Ile Gly Val
370 375 380

Ser Ser Val Ala Tyr Phe Ser Leu Arg Asn Ile Leu Glu Thr Glu Asn
385 390 395 400

Glu Asn Asp Ile Thr Gly Arg Met Arg Gly Lys Thr Val Lys Asn Asn
405 410 415

Lys Gly Glu Glu Lys Tyr Val Ser Gly Glu Val Asp Lys Ile Tyr Asn
420 425 430

Glu Asn Lys Gln Asn Glu Val Lys Glu Asn Leu Lys Met Phe Tyr Ser
435 440 445

Tyr Asp Phe Asn Met Asp Asn Lys Asn Glu Ile Glu Asp Phe Phe Ala
450 455 460

Asn Ile Asp Glu Ala Ile Ser Ser Ile Arg His Gly Ile Val His Phe
465 470 475 480

Asn Leu Glu Leu Glu Gly Lys Asp Ile Phe Ala Phe Lys Asn Ile Ala
485 490 495

Pro Ser Glu Ile Ser Lys Lys Met Phe Gln Asn Glu Ile Asn Glu Lys
500 505 510

Lys Leu Lys Leu Lys Ile Phe Lys Gln Leu Asn Ser Ala Asn Val Phe
515 520 525

Asn Tyr Tyr Glu Lys Asp Val Ile Ile Lys Tyr Leu Lys Asn Thr Lys
530 535 540

Phe Asn Phe Val Asn Lys Asn Ile Pro Phe Val Pro Ser Phe Thr Lys
545 550 555 560

Leu Tyr Asn Lys Ile Glu Asp Leu Arg Asn Thr Leu Lys Phe Phe Trp
565 570 575

Ser Val Pro Lys Asp Lys Glu Glu Lys Asp Ala Gln Ile Tyr Leu Leu
580 585 590

Lys Asn Ile Tyr Tyr Gly Glu Phe Leu Asn Lys Phe Val Lys Asn Ser
595 600 605

Lys Val Phe Phe Lys Ile Thr Asn Glu Val Ile Lys Ile Asn Lys Gln
610 615 620

Arg Asn Gln Lys Thr Gly His Tyr Lys Tyr Gln Lys Phe Glu Asn Ile
625 630 635 640

Glu Lys Thr Val Pro Val Glu Tyr Leu Ala Ile Ile Gln Ser Arg Glu
645 650 655

Met Ile Asn Asn Gln Asp Lys Glu Glu Lys Asn Thr Tyr Ile Asp Phe
660 665 670

Ile Gln Gln Ile Phe Leu Lys Gly Phe Ile Asp Tyr Leu Asn Lys Asn
675 680 685

Asn Leu Lys Tyr Ile Glu Ser Asn Asn Asn Asn Asp Asn Asn Asp Ile
690 695 700

Phe Ser Lys Ile Lys Ile Lys Lys Asp Asn Lys Glu Lys Tyr Asp Lys
705 710 715 720

Ile Leu Lys Asn Tyr Glu Lys His Asn Arg Asn Lys Glu Ile Pro His
725 730 735

Glu Ile Asn Glu Phe Val Arg Glu Ile Lys Leu Gly Lys Ile Leu Lys
740 745 750

Tyr Thr Glu Asn Leu Asn Met Phe Tyr Leu Ile Leu Lys Leu Leu Asn
755 760 765

His Lys Glu Leu Thr Asn Leu Lys Gly Ser Leu Glu Lys Tyr Gln Ser
770 775 780

Ala Asn Lys Glu Glu Thr Phe Ser Asp Glu Leu Glu Leu Ile Asn Leu
785 790 795 800

Leu Asn Leu Asp Asn Asn Arg Val Thr Glu Asp Phe Glu Leu Glu Ala
805 810 815

Asn Glu Ile Gly Lys Phe Leu Asp Phe Asn Glu Asn Lys Ile Lys Asp
820 825 830

Arg Lys Glu Leu Lys Lys Phe Asp Thr Asn Lys Ile Tyr Phe Asp Gly
835 840 845

Glu Asn Ile Ile Lys His Arg Ala Phe Tyr Asn Ile Lys Lys Tyr Gly
850 855 860

Met Leu Asn Leu Leu Glu Lys Ile Ala Asp Lys Ala Lys Tyr Lys Ile
865 870 875 880

Ser Leu Lys Glu Leu Lys Glu Tyr Ser Asn Lys Lys Asn Glu Ile Glu
885 890 895

Lys Asn Tyr Thr Met Gln Gln Asn Leu His Arg Lys Tyr Ala Arg Pro
900 905 910

Lys Lys Asp Glu Lys Phe Asn Asp Glu Asp Tyr Lys Glu Tyr Glu Lys
915 920 925

Ala Ile Gly Asn Ile Gln Lys Tyr Thr His Leu Lys Asn Lys Val Glu
930 935 940

Phe Asn Glu Leu Asn Leu Leu Gln Gly Leu Leu Leu Lys Ile Leu His
945 950 955 960

Arg Leu Val Gly Tyr Thr Ser Ile Trp Glu Arg Asp Leu Arg Phe Arg
965 970 975

Leu Lys Gly Glu Phe Pro Glu Asn His Tyr Ile Glu Glu Ile Phe Asn
980 985 990

Phe Asp Asn Ser Lys Asn Val Lys Tyr Lys Ser Gly Gln Ile Val Glu
995 1000 1005

Lys Tyr Ile Asn Phe Tyr Lys Glu Leu Tyr Lys Asp Asn Val Glu
1010 1015 1020

Lys Arg Ser Ile Tyr Ser Asp Lys Lys Val Lys Lys Leu Lys Gln
1025 1030 1035

Glu Lys Lys Asp Leu Tyr Ile Arg Asn Tyr Ile Ala His Phe Asn
1040 1045 1050

Tyr Ile Pro His Ala Glu Ile Ser Leu Leu Glu Val Leu Glu Asn
1055 1060 1065

Leu Arg Lys Leu Leu Ser Tyr Asp Arg Lys Leu Lys Asn Ala Ile
1070 1075 1080

Met Lys Ser Ile Val Asp Ile Leu Lys Glu Tyr Gly Phe Val Ala
1085 1090 1095

Thr Phe Lys Ile Gly Ala Asp Lys Lys Ile Glu Ile Gln Thr Leu
1100 1105 1110

Glu Ser Glu Lys Ile Val His Leu Lys Asn Leu Lys Lys Lys Lys
1115 1120 1125

Leu Met Thr Asp Arg Asn Ser Glu Glu Leu Cys Glu Leu Val Lys
1130 1135 1140

Val Met Phe Glu Tyr Lys Ala Leu Glu
1145 1150

<210> 52
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Lwa2Cas13a direct repeat

<400> 52
gatatagata accccaaaaa cgaagggatc taaaac

36

<210> 53
<211> 3858
<212> DNA
<213> Artificial Sequence

<220>
<223> RcsCas13a nucleic acid sequence

<400> 53
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ctgaagagaa agattagcac cgatggaaag aatcgcaagg aactgccagc acacctgtca

60

120

agtgatccaa aggccctgat tggacagtgg atctcaggga tcgacaaaat ctaccggaag	180
cccgatagta ggaaatccga tggcaaagca atccactccc caacccttag caaaatgcag	240
tttgacgcaa gggatgacct gggagaggca ttctggaaac tgggtgtcaga agctggcctg	300
gctcaggata gtgactatga tcagtttaag cggcgactgc atccatacgg agacaaattt	360
cagcctgctg atagcggagc aaaactgaag ttcgaagccg acccacctga gcctcaggcc	420
ttccacggca ggtggtatgg agcaatgtcc aagcgcggga atgacgcaaa ggagctggca	480
gtcgctctgt acgaacatct gcacgtcgat gagaaaagaa tcgatggcca gcctaagcgg	540
aatcctaaga ctgataaatt cgctccaggg ctggtggtgg ccgcgctct ggggattgag	600
tcaagcgtgc tgccaagagg aatggctaga ctggctagga attggggcga agaggaaatc	660
cagacttact ttgtcgtgga tgtggccgca tcagtgaagg aggtggctaa agctgctgtg	720
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gtggggttcg cactggcaga gcatctggaa agggtgacag gctccaagag gtgctcattc	840
gatcccgag ccggcccttc tgtcctggca ctgcacgacg aagtgaagaa aacttataaa	900
agactgtgcg cccggggaaa gaatgcagcc agagcttttc cagccgacaa gaccgaactg	960
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agtgccggcc agacagaaat caaagaaagc gagatctttg tcaggctgtg ggtgggagct	1140
tttgactggt ctgggcgcag catgaaagca tggattgacc caatggggaa gatcgtgaac	1200
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ctggatagac tgggggcaga gggaaatgaa ggcttcgtgt tcgctctgct gcgatacctg	1380
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atggcctacg	atcgcaaacg	caaaaacgca	gtcccacgga	gtatcctgga	tatgctggct	3300
cggctggggc	tgacactgaa	gtggcagatg	aaggaccacc	tgctgcagga	cgctacaatc	3360

acccaggctg caatcaaaca cctggataaa gtgcggctga ccgtgggggg ccccgccgcc 3420
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 agcgtgcaga accctaaacc acggcgccgg gatgatgggg acgcctggca caagccaccc 3540
 aagcctgcaa ctgctcagtc tcagcctgat cagaaacctc ccaacaaagc accttctgca 3600
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 catatctccc gcctgcgacg aatcagagag gacgccatca ttgtcgggcg gagatacaga 3780
 ttcagggtcg aaatctatgt ccccccaag agcaaacatt ccaaactgaa cgccgctgac 3840
 ctggtgcgaa ttgactga 3858

<210> 54
 <211> 1285
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> RcsCas13a amino acid sequence

<400> 54

Met Gln Ile Gly Lys Val Gln Gly Arg Thr Ile Ser Glu Phe Gly Asp
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Pro Ala Gly Gly Leu Lys Arg Lys Ile Ser Thr Asp Gly Lys Asn Arg
 20 25 30

Lys Glu Leu Pro Ala His Leu Ser Ser Asp Pro Lys Ala Leu Ile Gly
 35 40 45

Gln Trp Ile Ser Gly Ile Asp Lys Ile Tyr Arg Lys Pro Asp Ser Arg
 50 55 60

Lys Ser Asp Gly Lys Ala Ile His Ser Pro Thr Pro Ser Lys Met Gln
 65 70 75 80

Phe Asp Ala Arg Asp Asp Leu Gly Glu Ala Phe Trp Lys Leu Val Ser
 85 90 95

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

Leu His Pro Tyr Gly Asp Lys Phe Gln Pro Ala Asp Ser Gly Ala Lys
115 120 125

Leu Lys Phe Glu Ala Asp Pro Pro Glu Pro Gln Ala Phe His Gly Arg
130 135 140

Trp Tyr Gly Ala Met Ser Lys Arg Gly Asn Asp Ala Lys Glu Leu Ala
145 150 155 160

Val Ala Leu Tyr Glu His Leu His Val Asp Glu Lys Arg Ile Asp Gly
165 170 175

Gln Pro Lys Arg Asn Pro Lys Thr Asp Lys Phe Ala Pro Gly Leu Val
180 185 190

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

Ala Arg Leu Ala Arg Asn Trp Gly Glu Glu Glu Ile Gln Thr Tyr Phe
210 215 220

Val Val Asp Val Ala Ala Ser Val Lys Glu Val Ala Lys Ala Ala Val
225 230 235 240

Ser Ala Ala Gln Ala Phe Asp Pro Pro Arg Gln Val Ser Gly Arg Ser
245 250 255

Leu Ser Pro Lys Val Gly Phe Ala Leu Ala Glu His Leu Glu Arg Val
260 265 270

Thr Gly Ser Lys Arg Cys Ser Phe Asp Pro Ala Ala Gly Pro Ser Val
275 280 285

Leu Ala Leu His Asp Glu Val Lys Lys Thr Tyr Lys Arg Leu Cys Ala
290 295 300

Arg Gly Lys Asn Ala Ala Arg Ala Phe Pro Ala Asp Lys Thr Glu Leu
305 310 315 320

Leu Ala Leu Met Arg His Thr His Glu Asn Arg Val Arg Asn Gln Met
325 330 335

Val Arg Met Gly Arg Val Ser Glu Tyr Arg Gly Gln Gln Ala Gly Asp
340 345 350

Leu Ala Gln Ser His Tyr Trp Thr Ser Ala Gly Gln Thr Glu Ile Lys
355 360 365

Glu Ser Glu Ile Phe Val Arg Leu Trp Val Gly Ala Phe Ala Leu Ala
370 375 380

Gly Arg Ser Met Lys Ala Trp Ile Asp Pro Met Gly Lys Ile Val Asn
385 390 395 400

Thr Glu Lys Asn Asp Arg Asp Leu Thr Ala Ala Val Asn Ile Arg Gln
405 410 415

Val Ile Ser Asn Lys Glu Met Val Ala Glu Ala Met Ala Arg Arg Gly
420 425 430

Ile Tyr Phe Gly Glu Thr Pro Glu Leu Asp Arg Leu Gly Ala Glu Gly
435 440 445

Asn Glu Gly Phe Val Phe Ala Leu Leu Arg Tyr Leu Arg Gly Cys Arg
450 455 460

Asn Gln Thr Phe His Leu Gly Ala Arg Ala Gly Phe Leu Lys Glu Ile
465 470 475 480

Arg Lys Glu Leu Glu Lys Thr Arg Trp Gly Lys Ala Lys Glu Ala Glu
485 490 495

His Val Val Leu Thr Asp Lys Thr Val Ala Ala Ile Arg Ala Ile Ile
500 505 510

Asp Asn Asp Ala Lys Ala Leu Gly Ala Arg Leu Leu Ala Asp Leu Ser
515 520 525

Gly Ala Phe Val Ala His Tyr Ala Ser Lys Glu His Phe Ser Thr Leu
530 535 540

Tyr Ser Glu Ile Val Lys Ala Val Lys Asp Ala Pro Glu Val Ser Ser
545 550 555 560

Gly Leu Pro Arg Leu Lys Leu Leu Leu Lys Arg Ala Asp Gly Val Arg
565 570 575

Gly Tyr Val His Gly Leu Arg Asp Thr Arg Lys His Ala Phe Ala Thr
580 585 590

Lys Leu Pro Pro Pro Pro Ala Pro Arg Glu Leu Asp Asp Pro Ala Thr
595 600 605

Lys Ala Arg Tyr Ile Ala Leu Leu Arg Leu Tyr Asp Gly Pro Phe Arg
610 615 620

Ala Tyr Ala Ser Gly Ile Thr Gly Thr Ala Leu Ala Gly Pro Ala Ala
625 630 635 640

Arg Ala Lys Glu Ala Ala Thr Ala Leu Ala Gln Ser Val Asn Val Thr
645 650 655

Lys Ala Tyr Ser Asp Val Met Glu Gly Arg Thr Ser Arg Leu Arg Pro
660 665 670

Pro Asn Asp Gly Glu Thr Leu Arg Glu Tyr Leu Ser Ala Leu Thr Gly
675 680 685

Glu Thr Ala Thr Glu Phe Arg Val Gln Ile Gly Tyr Glu Ser Asp Ser
690 695 700

Glu Asn Ala Arg Lys Gln Ala Glu Phe Ile Glu Asn Tyr Arg Arg Asp
705 710 715 720

Met Leu Ala Phe Met Phe Glu Asp Tyr Ile Arg Ala Lys Gly Phe Asp
725 730 735

Trp Ile Leu Lys Ile Glu Pro Gly Ala Thr Ala Met Thr Arg Ala Pro
740 745 750

Val Leu Pro Glu Pro Ile Asp Thr Arg Gly Gln Tyr Glu His Trp Gln
755 760 765

Ala Ala Leu Tyr Leu Val Met His Phe Val Pro Ala Ser Asp Val Ser
770 775 780

Asn Leu Leu His Gln Leu Arg Lys Trp Glu Ala Leu Gln Gly Lys Tyr
785 790 795 800

Glu Leu Val Gln Asp Gly Asp Ala Thr Asp Gln Ala Asp Ala Arg Arg
805 810 815

Glu Ala Leu Asp Leu Val Lys Arg Phe Arg Asp Val Leu Val Leu Phe
820 825 830

Leu Lys Thr Gly Glu Ala Arg Phe Glu Gly Arg Ala Ala Pro Phe Asp
835 840 845

Leu Lys Pro Phe Arg Ala Leu Phe Ala Asn Pro Ala Thr Phe Asp Arg
850 855 860

Leu Phe Met Ala Thr Pro Thr Thr Ala Arg Pro Ala Glu Asp Asp Pro
865 870 875 880

Glu Gly Asp Gly Ala Ser Glu Pro Glu Leu Arg Val Ala Arg Thr Leu
885 890 895

Arg Gly Leu Arg Gln Ile Ala Arg Tyr Asn His Met Ala Val Leu Ser
900 905 910

Asp Leu Phe Ala Lys His Lys Val Arg Asp Glu Glu Val Ala Arg Leu
915 920 925

Ala Glu Ile Glu Asp Glu Thr Gln Glu Lys Ser Gln Ile Val Ala Ala
930 935 940

Gln Glu Leu Arg Thr Asp Leu His Asp Lys Val Met Lys Cys His Pro
945 950 955 960

Lys Thr Ile Ser Pro Glu Glu Arg Gln Ser Tyr Ala Ala Ala Ile Lys
965 970 975

Thr Ile Glu Glu His Arg Phe Leu Val Gly Arg Val Tyr Leu Gly Asp
980 985 990

His Leu Arg Leu His Arg Leu Met Met Asp Val Ile Gly Arg Leu Ile
995 1000 1005

Asp Tyr Ala Gly Ala Tyr Glu Arg Asp Thr Gly Thr Phe Leu Ile
1010 1015 1020

Asn Ala Ser Lys Gln Leu Gly Ala Gly Ala Asp Trp Ala Val Thr
1025 1030 1035

Ile Ala Gly Ala Ala Asn Thr Asp Ala Arg Thr Gln Thr Arg Lys
1040 1045 1050

Asp Leu Ala His Phe Asn Val Leu Asp Arg Ala Asp Gly Thr Pro
1055 1060 1065

Asp Leu Thr Ala Leu Val Asn Arg Ala Arg Glu Met Met Ala Tyr
1070 1075 1080

Asp Arg Lys Arg Lys Asn Ala Val Pro Arg Ser Ile Leu Asp Met
1085 1090 1095

Leu Ala Arg Leu Gly Leu Thr Leu Lys Trp Gln Met Lys Asp His
1100 1105 1110

Leu Leu Gln Asp Ala Thr Ile Thr Gln Ala Ala Ile Lys His Leu
1115 1120 1125

Asp Lys Val Arg Leu Thr Val Gly Gly Pro Ala Ala Val Thr Glu
1130 1135 1140

Ala Arg Phe Ser Gln Asp Tyr Leu Gln Met Val Ala Ala Val Phe
1145 1150 1155

Asn Gly Ser Val Gln Asn Pro Lys Pro Arg Arg Arg Asp Asp Gly
1160 1165 1170

Asp Ala Trp His Lys Pro Pro Lys Pro Ala Thr Ala Gln Ser Gln
 1175 1180 1185

Pro Asp Gln Lys Pro Pro Asn Lys Ala Pro Ser Ala Gly Ser Arg
 1190 1195 1200

Leu Pro Pro Pro Gln Val Gly Glu Val Tyr Glu Gly Val Val Val
 1205 1210 1215

Lys Val Ile Asp Thr Gly Ser Leu Gly Phe Leu Ala Val Glu Gly
 1220 1225 1230

Val Ala Gly Asn Ile Gly Leu His Ile Ser Arg Leu Arg Arg Ile
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Arg Glu Asp Ala Ile Ile Val Gly Arg Arg Tyr Arg Phe Arg Val
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Glu Ile Tyr Val Pro Pro Lys Ser Asn Thr Ser Lys Leu Asn Ala
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Ala Asp Leu Val Arg Ile Asp
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<400> 55
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36

<210> 56
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<220>
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<400> 56

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 <212> PRT
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 <223> RcrCas13a amino acid sequence

 <400> 57

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Lys	Glu	Leu	Pro	Ala	His	Leu	Ser	Ser	Asp	Pro	Lys	Ala	Leu	Ile	Gly
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Gln	Trp	Ile	Ser	Gly	Ile	Asp	Lys	Ile	Tyr	Arg	Lys	Pro	Asp	Ser	Arg
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Lys	Ser	Asp	Gly	Lys	Ala	Ile	His	Ser	Pro	Thr	Pro	Ser	Lys	Met	Gln
65					70					75				80	

Phe Asp Ala Arg Asp Asp Leu Gly Glu Ala Phe Trp Lys Leu Val Ser
85 90 95

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

Leu His Pro Tyr Gly Asp Lys Phe Gln Pro Ala Asp Ser Gly Ala Lys
115 120 125

Leu Lys Phe Glu Ala Asp Pro Pro Glu Pro Gln Ala Phe His Gly Arg
130 135 140

Trp Tyr Gly Ala Met Ser Lys Arg Gly Asn Asp Ala Lys Glu Leu Ala
145 150 155 160

Ala Ala Leu Tyr Glu His Leu His Val Asp Glu Lys Arg Ile Asp Gly
165 170 175

Gln Pro Lys Arg Asn Pro Lys Thr Asp Lys Phe Ala Pro Gly Leu Val
180 185 190

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

Ala Arg Leu Ala Arg Asn Trp Gly Glu Glu Glu Ile Gln Thr Tyr Phe
210 215 220

Val Val Asp Val Ala Ala Ser Val Lys Glu Val Ala Lys Ala Ala Val
225 230 235 240

Ser Ala Ala Gln Ala Phe Asp Pro Pro Arg Gln Val Ser Gly Arg Ser
245 250 255

Leu Ser Pro Lys Val Gly Phe Ala Leu Ala Glu His Leu Glu Arg Val
260 265 270

Thr Gly Ser Lys Arg Cys Ser Phe Asp Pro Ala Ala Gly Pro Ser Val
275 280 285

Leu Ala Leu His Asp Glu Val Lys Lys Thr Tyr Lys Arg Leu Cys Ala
290 295 300

Arg Gly Lys Asn Ala Ala Arg Ala Phe Pro Ala Asp Lys Thr Glu Leu
305 310 315 320

Leu Ala Leu Met Arg His Thr His Glu Asn Arg Val Arg Asn Gln Met
325 330 335

Val Arg Met Gly Arg Val Ser Glu Tyr Arg Gly Gln Gln Ala Gly Asp
340 345 350

Leu Ala Gln Ser His Tyr Trp Thr Ser Ala Gly Gln Thr Glu Ile Lys
355 360 365

Glu Ser Glu Ile Phe Val Arg Leu Trp Val Gly Ala Phe Ala Leu Ala
370 375 380

Gly Arg Ser Met Lys Ala Trp Ile Asp Pro Met Gly Lys Ile Val Asn
385 390 395 400

Thr Glu Lys Asn Asp Arg Asp Leu Thr Ala Ala Val Asn Ile Arg Gln
405 410 415

Val Ile Ser Asn Lys Glu Met Val Ala Glu Ala Met Ala Arg Arg Gly
420 425 430

Ile Tyr Phe Gly Glu Thr Pro Glu Leu Asp Arg Leu Gly Ala Glu Gly
435 440 445

Asn Glu Gly Phe Val Phe Ala Leu Leu Arg Tyr Leu Arg Gly Cys Arg
450 455 460

Asn Gln Thr Phe His Leu Gly Ala Arg Ala Gly Phe Leu Lys Glu Ile
465 470 475 480

Arg Lys Glu Leu Glu Lys Thr Arg Trp Gly Lys Ala Lys Glu Ala Glu
485 490 495

His Val Val Leu Thr Asp Lys Thr Val Ala Ala Ile Arg Ala Ile Ile
500 505 510

Asp Asn Asp Ala Lys Ala Leu Gly Ala Arg Leu Leu Ala Asp Leu Ser
515 520 525

Gly Ala Phe Val Ala His Tyr Ala Ser Lys Glu His Phe Ser Thr Leu
530 535 540

Tyr Ser Glu Ile Val Lys Ala Val Lys Asp Ala Pro Glu Val Ser Ser
545 550 555 560

Gly Leu Pro Arg Leu Lys Leu Leu Leu Lys Arg Ala Asp Gly Val Arg
565 570 575

Gly Tyr Val His Gly Leu Arg Asp Thr Arg Lys His Ala Phe Ala Thr
580 585 590

Lys Leu Pro Pro Pro Pro Ala Pro Arg Glu Leu Asp Asp Pro Ala Thr
595 600 605

Lys Ala Arg Tyr Ile Ala Leu Leu Arg Leu Tyr Asp Gly Pro Phe Arg
610 615 620

Ala Tyr Ala Ser Gly Ile Thr Gly Thr Ala Leu Ala Gly Pro Ala Ala
625 630 635 640

Arg Ala Lys Glu Ala Ala Thr Ala Leu Ala Gln Ser Val Asn Val Thr
645 650 655

Lys Ala Tyr Ser Asp Val Met Glu Gly Arg Ser Ser Arg Leu Arg Pro
660 665 670

Pro Asn Asp Gly Glu Thr Leu Arg Glu Tyr Leu Ser Ala Leu Thr Gly
675 680 685

Glu Thr Ala Thr Glu Phe Arg Val Gln Ile Gly Tyr Glu Ser Asp Ser
690 695 700

Glu Asn Ala Arg Lys Gln Ala Glu Phe Ile Glu Asn Tyr Arg Arg Asp
705 710 715 720

Met Leu Ala Phe Met Phe Glu Asp Tyr Ile Arg Ala Lys Gly Phe Asp
725 730 735

Trp Ile Leu Lys Ile Glu Pro Gly Ala Thr Ala Met Thr Arg Ala Pro
740 745 750

Val Leu Pro Glu Pro Ile Asp Thr Arg Gly Gln Tyr Glu His Trp Gln
755 760 765

Ala Ala Leu Tyr Leu Val Met His Phe Val Pro Ala Ser Asp Val Ser
770 775 780

Asn Leu Leu His Gln Leu Arg Lys Trp Glu Ala Leu Gln Gly Lys Tyr
785 790 795 800

Glu Leu Val Gln Asp Gly Asp Ala Thr Asp Gln Ala Asp Ala Arg Arg
805 810 815

Glu Ala Leu Asp Leu Val Lys Arg Phe Arg Asp Val Leu Val Leu Phe
820 825 830

Leu Lys Thr Gly Glu Ala Arg Phe Glu Gly Arg Ala Ala Pro Phe Asp
835 840 845

Leu Lys Pro Phe Arg Ala Leu Phe Ala Asn Pro Ala Thr Phe Asp Arg
850 855 860

Leu Phe Met Ala Thr Pro Thr Thr Ala Arg Pro Ala Glu Asp Asp Pro
865 870 875 880

Glu Gly Asp Gly Ala Ser Glu Pro Glu Leu Arg Val Ala Arg Thr Leu
885 890 895

Arg Gly Leu Arg Gln Ile Ala Arg Tyr Asn His Met Ala Val Leu Ser
900 905 910

Asp Leu Phe Ala Lys His Lys Val Arg Asp Glu Glu Val Ala Arg Leu
915 920 925

Ala Glu Ile Glu Asp Glu Thr Gln Glu Lys Ser Gln Ile Val Ala Ala
930 935 940

Gln Glu Leu Arg Thr Asp Leu His Asp Lys Val Met Lys Cys His Pro
945 950 955 960

Lys Thr Ile Ser Pro Glu Glu Arg Gln Ser Tyr Ala Ala Ala Ile Lys
965 970 975

Thr Ile Glu Glu His Arg Phe Leu Val Gly Arg Val Tyr Leu Gly Asp
980 985 990

His Leu Arg Leu His Arg Leu Met Met Asp Val Ile Gly Arg Leu Ile
995 1000 1005

Asp Tyr Ala Gly Ala Tyr Glu Arg Asp Thr Gly Thr Phe Leu Ile
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Asn Ala Ser Lys Gln Leu Gly Ala Gly Ala Asp Trp Ala Val Thr
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Ile Ala Gly Ala Ala Asn Thr Gly Ala Arg Thr Gln Thr Arg Lys
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Asp Leu Ala His Phe Asn Val Leu Asp Arg Ala Asp Gly Thr Pro
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Asp Leu Thr Ala Leu Val Asn Arg Ala Arg Glu Met Met Ala Tyr
1070 1075 1080

Asp Arg Lys Arg Lys Asn Ala Val Pro Arg Ser Ile Leu Asp Met
1085 1090 1095

Leu Ala Arg Leu Gly Leu Thr Leu Lys Trp Gln Met Lys Asp His
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Leu Leu Gln Asp Ala Thr Ile Thr Gln Ala Ala Ile Lys His Leu
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Asp Lys Val Arg Leu Thr Val Gly Gly Pro Ala Ala Val Thr Glu
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Ala Arg Phe Ser Gln Asp Tyr Leu Gln Met Val Ala Ala Val Phe
1145 1150 1155

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 1160 1165 1170

Asp Ala Trp His Lys Pro Pro Lys Pro Ala Thr Ala Gln Ser Gln
 1175 1180 1185

Pro Asp Gln Lys Pro Pro Asn Lys Ala Pro Ser Ala Gly Ser Arg
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Leu Pro Pro Pro Gln Val Gly Glu Val Tyr Glu Gly Val Val Val
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Lys Val Ile Asp Thr Gly Ser Leu Gly Phe Leu Ala Val Glu Gly
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Val Ala Gly Asn Ile Gly Leu His Ile Ser Arg Leu Arg Arg Ile
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Arg Glu Asp Ala Ile Ile Val Gly Arg Arg Tyr Arg Phe Trp Val
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Glu Ile Tyr Val Pro Pro Lys Ser Asn Thr Ser Lys Leu Asn Ala
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Ala Asp Leu Val Arg Ile Asp
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36

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<223> RcdCas13a nucleic acid sequence

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<212> PRT
<213> Artificial Sequence

<220>
<223> RcdCas13a amino acid sequence

<400> 60

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Lys Glu Leu Pro Ala His Leu Ser Ser Asp Pro Lys Ala Leu Ile Gly
35 40 45

Gln Trp Ile Ser Gly Ile Asp Lys Ile Tyr Arg Lys Pro Asp Ser Arg
50 55 60

Lys Ser Asp Gly Lys Ala Ile His Ser Pro Thr Pro Ser Lys Met Gln
65 70 75 80

Phe Asp Ala Arg Asp Asp Leu Gly Glu Ala Phe Trp Lys Leu Val Ser
85 90 95

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

Leu His Pro Tyr Gly Asp Lys Phe Gln Pro Ala Asp Ser Gly Ala Lys
115 120 125

Leu Lys Phe Glu Ala Asp Pro Pro Glu Pro Gln Ala Phe His Gly Arg
130 135 140

Trp Tyr Gly Ala Met Ser Lys Arg Gly Asn Asp Ala Lys Glu Leu Ala
145 150 155 160

Ala Ala Leu Tyr Glu His Leu His Val Asp Glu Lys Arg Ile Asp Gly
165 170 175

Gln Pro Lys Arg Asn Pro Lys Thr Asp Lys Phe Ala Pro Gly Leu Val
180 185 190

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

Ala Arg Leu Ala Arg Asn Trp Gly Glu Glu Glu Ile Gln Thr Tyr Phe
210 215 220

Val Val Asp Val Ala Ala Ser Val Lys Glu Val Ala Lys Ala Ala Val
225 230 235 240

Ser Ala Ala Gln Ala Phe Asp Pro Pro Arg Gln Val Ser Gly Arg Ser
245 250 255

Leu Ser Pro Lys Val Gly Phe Ala Leu Ala Glu His Leu Glu Arg Val
260 265 270

Thr Gly Ser Lys Arg Cys Ser Phe Asp Pro Ala Ala Gly Pro Ser Val
275 280 285

Leu Ala Leu His Asp Glu Val Lys Lys Thr Tyr Lys Arg Leu Cys Ala
290 295 300

Arg Gly Lys Asn Ala Ala Arg Ala Phe Pro Ala Asp Lys Thr Glu Leu
305 310 315 320

Leu Ala Leu Met Arg His Thr His Glu Asn Arg Val Arg Asn Gln Met
325 330 335

Val Arg Met Gly Arg Val Ser Glu Tyr Arg Gly Gln Gln Ala Gly Asp
340 345 350

Leu Ala Gln Ser His Tyr Trp Thr Ser Ala Gly Gln Thr Glu Ile Lys
355 360 365

Glu Ser Glu Ile Phe Val Arg Leu Trp Val Gly Ala Phe Ala Leu Ala
370 375 380

Gly Arg Ser Met Lys Ala Trp Ile Asp Pro Met Gly Lys Ile Val Asn
385 390 395 400

Thr Glu Lys Asn Asp Arg Asp Leu Thr Ala Ala Val Asn Ile Arg Gln
405 410 415

Val Ile Ser Asn Lys Glu Met Val Ala Glu Ala Met Ala Arg Arg Gly
420 425 430

Ile Tyr Phe Gly Glu Thr Pro Glu Leu Asp Arg Leu Gly Ala Glu Gly
435 440 445

Asn Glu Gly Phe Val Phe Ala Leu Leu Arg Tyr Leu Arg Gly Cys Arg
450 455 460

Asn Gln Thr Phe His Leu Gly Ala Arg Ala Gly Phe Leu Lys Glu Ile
465 470 475 480

Arg Lys Glu Leu Glu Lys Thr Arg Trp Gly Lys Ala Lys Glu Ala Glu
485 490 495

His Val Val Leu Thr Asp Lys Thr Val Ala Ala Ile Arg Ala Ile Ile
500 505 510

Asp Asn Asp Ala Lys Ala Leu Gly Ala Arg Leu Leu Ala Asp Leu Ser
515 520 525

Gly Ala Phe Val Ala His Tyr Ala Ser Lys Glu His Phe Ser Thr Leu
530 535 540

Tyr Ser Glu Ile Val Lys Ala Val Lys Asp Ala Pro Glu Val Ser Ser
545 550 555 560

Gly Leu Pro Arg Leu Lys Leu Leu Leu Lys Arg Ala Asp Gly Val Arg
565 570 575

Gly Tyr Val His Gly Leu Arg Asp Thr Arg Lys His Ala Phe Ala Thr
580 585 590

Lys Leu Pro Pro Pro Pro Ala Pro Arg Glu Leu Asp Asp Pro Ala Thr
595 600 605

Lys Ala Arg Tyr Ile Ala Leu Leu Arg Leu Tyr Asp Gly Pro Phe Arg
610 615 620

Ala Tyr Ala Ser Gly Ile Thr Gly Thr Ala Leu Ala Gly Pro Ala Ala
625 630 635 640

Arg Ala Lys Glu Ala Ala Thr Ala Leu Ala Gln Ser Val Asn Val Thr
645 650 655

Lys Ala Tyr Ser Asp Val Met Glu Gly Arg Ser Ser Arg Leu Arg Pro
660 665 670

Pro Asn Asp Gly Glu Thr Leu Arg Glu Tyr Leu Ser Ala Leu Thr Gly
675 680 685

Glu Thr Ala Thr Glu Phe Arg Val Gln Ile Gly Tyr Glu Ser Asp Ser
690 695 700

Glu Asn Ala Arg Lys Gln Ala Glu Phe Ile Glu Asn Tyr Arg Arg Asp
705 710 715 720

Met Leu Ala Phe Met Phe Glu Asp Tyr Ile Arg Ala Lys Gly Phe Asp
725 730 735

Trp Ile Leu Lys Ile Glu Pro Gly Ala Thr Ala Met Thr Arg Ala Pro
740 745 750

Val Leu Pro Glu Pro Ile Asp Thr Arg Gly Gln Tyr Glu His Trp Gln
755 760 765

Ala Ala Leu Tyr Leu Val Met His Phe Val Pro Ala Ser Asp Val Ser
770 775 780

Asn Leu Leu His Gln Leu Arg Lys Trp Glu Ala Leu Gln Gly Lys Tyr
785 790 795 800

Glu Leu Val Gln Asp Gly Asp Ala Thr Asp Gln Ala Asp Ala Arg Arg
805 810 815

Glu Ala Leu Asp Leu Val Lys Arg Phe Arg Asp Val Leu Val Leu Phe
820 825 830

Leu Lys Thr Gly Glu Ala Arg Phe Glu Gly Arg Ala Ala Pro Phe Asp
835 840 845

Leu Lys Pro Phe Arg Ala Leu Phe Ala Asn Pro Ala Thr Phe Asp Arg
850 855 860

Leu Phe Met Ala Thr Pro Thr Thr Ala Arg Pro Ala Glu Asp Asp Pro
865 870 875 880

Glu Gly Asp Gly Ala Ser Glu Pro Glu Leu Arg Val Ala Arg Thr Leu
885 890 895

Arg Gly Leu Arg Gln Ile Ala Arg Tyr Asn His Met Ala Val Leu Ser
900 905 910

Asp Leu Phe Ala Lys His Lys Val Arg Asp Glu Glu Val Ala Arg Leu
915 920 925

Ala Glu Ile Glu Asp Glu Thr Gln Glu Lys Ser Gln Ile Val Ala Ala
930 935 940

Gln Glu Leu Arg Thr Asp Leu His Asp Lys Val Met Lys Cys His Pro
945 950 955 960

Lys Thr Ile Ser Pro Glu Glu Arg Gln Ser Tyr Ala Ala Ala Ile Lys
965 970 975

Thr Ile Glu Glu His Arg Phe Leu Val Gly Arg Val Tyr Leu Gly Asp
980 985 990

His Leu Arg Leu His Arg Leu Met Met Asp Val Ile Gly Arg Leu Ile
995 1000 1005

Asp Tyr Ala Gly Ala Tyr Glu Arg Asp Thr Gly Thr Phe Leu Ile
1010 1015 1020

Asn Ala Ser Lys Gln Leu Gly Ala Gly Ala Asp Trp Ala Val Thr
1025 1030 1035

Ile Ala Gly Ala Ala Asn Thr Asp Ala Arg Thr Gln Thr Arg Lys
1040 1045 1050

Asp Leu Ala His Phe Asn Val Leu Asp Arg Ala Asp Gly Thr Pro
1055 1060 1065

Asp Leu Thr Ala Leu Val Asn Arg Ala Arg Glu Met Met Ala Tyr
1070 1075 1080

Asp Arg Lys Arg Lys Asn Ala Val Pro Arg Ser Ile Leu Asp Met
1085 1090 1095

Leu Ala Arg Leu Gly Leu Thr Leu Lys Trp Gln Met Lys Asp His
1100 1105 1110

Leu Leu Gln Asp Ala Thr Ile Thr Gln Ala Ala Ile Lys His Leu
1115 1120 1125

Asp Lys Val Arg Leu Thr Val Gly Gly Pro Ala Ala Val Thr Glu
1130 1135 1140

Ala Arg Phe Ser Gln Asp Tyr Leu Gln Met Val Ala Ala Val Phe
 1145 1150 1155

Asn Gly Ser Val Gln Asn Pro Lys Pro Arg Arg Arg Asp Asp Gly
 1160 1165 1170

Asp Ala Trp His Lys Pro Pro Lys Pro Ala Thr Ala Gln Ser Gln
 1175 1180 1185

Pro Asp Gln Lys Pro Pro Asn Lys Ala Pro Ser Ala Gly Ser Arg
 1190 1195 1200

Leu Pro Pro Pro Gln Val Gly Glu Val Tyr Glu Gly Val Val Val
 1205 1210 1215

Lys Val Ile Asp Thr Gly Ser Leu Gly Phe Leu Ala Val Glu Gly
 1220 1225 1230

Val Ala Gly Asn Ile Gly Leu His Ile Ser Arg Leu Arg Arg Ile
 1235 1240 1245

Arg Glu Asp Ala Ile Ile Val Gly Arg Arg Tyr Arg Phe Arg Val
 1250 1255 1260

Glu Ile Tyr Val Pro Pro Lys Ser Asn Thr Ser Lys Leu Asn Ala
 1265 1270 1275

Ala Asp Leu Val Arg Ile Asp
 1280 1285

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 <213> Artificial Sequence

<220>
 <223> RcdCas13a direct repeat

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<210> 62
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<212> DNA
<213> Artificial Sequence

<220>
<223> PguCas13b nucleic acid sequence

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gaccggcagc tggcctacag caaggccgac atcaccaacg accaggacgt gctgagcttc 180
aaggccctgt ggaagaactt cgacaacgac ctggaaagaa agagccggct gcggagcctg 240
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<212> PRT
<213> Artificial Sequence

<220>
<223> PguCas13b amino acid sequence

<400> 63

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Glu Asp Lys His Phe Trp Ala Ala Phe Leu Asn Leu Ala Arg His Asn
20 25 30

Ala Tyr Ile Thr Leu Thr His Ile Asp Arg Gln Leu Ala Tyr Ser Lys
35 40 45

Ala Asp Ile Thr Asn Asp Gln Asp Val Leu Ser Phe Lys Ala Leu Trp
50 55 60

Lys Asn Phe Asp Asn Asp Leu Glu Arg Lys Ser Arg Leu Arg Ser Leu
65 70 75 80

Ile Leu Lys His Phe Ser Phe Leu Glu Gly Ala Ala Tyr Gly Lys Lys
85 90 95

Leu Phe Glu Ser Lys Ser Ser Gly Asn Lys Ser Ser Lys Asn Lys Glu
100 105 110

Leu Thr Lys Lys Glu Lys Glu Glu Leu Gln Ala Asn Ala Leu Ser Leu
115 120 125

Asp Asn Leu Lys Ser Ile Leu Phe Asp Phe Leu Gln Lys Leu Lys Asp
130 135 140

Phe Arg Asn Tyr Tyr Ser His Tyr Arg His Ser Gly Ser Ser Glu Leu
145 150 155 160

Pro Leu Phe Asp Gly Asn Met Leu Gln Arg Leu Tyr Asn Val Phe Asp
165 170 175

Val Ser Val Gln Arg Val Lys Ile Asp His Glu His Asn Asp Glu Val
180 185 190

Asp Pro His Tyr His Phe Asn His Leu Val Arg Lys Gly Lys Lys Asp
195 200 205

Arg Tyr Gly His Asn Asp Asn Pro Ser Phe Lys His His Phe Val Asp
210 215 220

Gly Glu Gly Met Val Thr Glu Ala Gly Leu Leu Phe Phe Val Ser Leu
225 230 235 240

Phe Leu Glu Lys Arg Asp Ala Ile Trp Met Gln Lys Lys Ile Arg Gly
245 250 255

Phe Lys Gly Gly Thr Glu Thr Tyr Gln Gln Met Thr Asn Glu Val Phe
260 265 270

Cys Arg Ser Arg Ile Ser Leu Pro Lys Leu Lys Leu Glu Ser Leu Arg
275 280 285

Met Asp Asp Trp Met Leu Leu Asp Met Leu Asn Glu Leu Val Arg Cys
290 295 300

Pro Lys Pro Leu Tyr Asp Arg Leu Arg Glu Asp Asp Arg Ala Cys Phe
305 310 315 320

Arg Val Pro Val Asp Ile Leu Pro Asp Glu Asp Asp Thr Asp Gly Gly
325 330 335

Gly Glu Asp Pro Phe Lys Asn Thr Leu Val Arg His Gln Asp Arg Phe
340 345 350

Pro Tyr Phe Ala Leu Arg Tyr Phe Asp Leu Lys Lys Val Phe Thr Ser
355 360 365

Leu Arg Phe His Ile Asp Leu Gly Thr Tyr His Phe Ala Ile Tyr Lys
370 375 380

Lys Met Ile Gly Glu Gln Pro Glu Asp Arg His Leu Thr Arg Asn Leu
385 390 395 400

Tyr Gly Phe Gly Arg Ile Gln Asp Phe Ala Glu Glu His Arg Pro Glu
405 410 415

Glu Trp Lys Arg Leu Val Arg Asp Leu Asp Tyr Phe Glu Thr Gly Asp
420 425 430

Lys Pro Tyr Ile Ser Gln Thr Ser Pro His Tyr His Ile Glu Lys Gly
435 440 445

Lys Ile Gly Leu Arg Phe Met Pro Glu Gly Gln His Leu Trp Pro Ser
450 455 460

Pro Glu Val Gly Thr Thr Arg Thr Gly Arg Ser Lys Tyr Ala Gln Asp
465 470 475 480

Lys Arg Leu Thr Ala Glu Ala Phe Leu Ser Val His Glu Leu Met Pro
485 490 495

Met Met Phe Tyr Tyr Phe Leu Leu Arg Glu Lys Tyr Ser Glu Glu Val
500 505 510

Ser Ala Glu Arg Val Gln Gly Arg Ile Lys Arg Val Ile Glu Asp Val
515 520 525

Tyr Ala Val Tyr Asp Ala Phe Ala Arg Asp Glu Ile Asn Thr Arg Asp
530 535 540

Glu Leu Asp Ala Cys Leu Ala Asp Lys Gly Ile Arg Arg Gly His Leu
545 550 555 560

Pro Arg Gln Met Ile Ala Ile Leu Ser Gln Glu His Lys Asp Met Glu
565 570 575

Glu Lys Ile Arg Lys Lys Leu Gln Glu Met Met Ala Asp Thr Asp His
580 585 590

Arg Leu Asp Met Leu Asp Arg Gln Thr Asp Arg Lys Ile Arg Ile Gly
595 600 605

Arg Lys Asn Ala Gly Leu Pro Lys Ser Gly Val Ile Ala Asp Trp Leu
610 615 620

Val Arg Asp Met Met Arg Phe Gln Pro Val Ala Lys Asp Ala Ser Gly
625 630 635 640

Lys Pro Leu Asn Asn Ser Lys Ala Asn Ser Thr Glu Tyr Arg Met Leu
645 650 655

Gln Arg Ala Leu Ala Leu Phe Gly Gly Glu Lys Glu Arg Leu Thr Pro
660 665 670

Tyr Phe Arg Gln Met Asn Leu Thr Gly Gly Asn Asn Pro His Pro Phe
675 680 685

Leu His Glu Thr Arg Trp Glu Ser His Thr Asn Ile Leu Ser Phe Tyr
690 695 700

Arg Ser Tyr Leu Arg Ala Arg Lys Ala Phe Leu Glu Arg Ile Gly Arg
705 710 715 720

Ser Asp Arg Val Glu Asn Arg Pro Phe Leu Leu Leu Lys Glu Pro Lys
725 730 735

Thr Asp Arg Gln Thr Leu Val Ala Gly Trp Lys Gly Glu Phe His Leu
740 745 750

Pro Arg Gly Ile Phe Thr Glu Ala Val Arg Asp Cys Leu Ile Glu Met
755 760 765

Gly His Asp Glu Val Ala Ser Tyr Lys Glu Val Gly Phe Met Ala Lys
770 775 780

Ala Val Pro Leu Tyr Phe Glu Arg Ala Cys Glu Asp Arg Val Gln Pro
785 790 795 800

Phe Tyr Asp Ser Pro Phe Asn Val Gly Asn Ser Leu Lys Pro Lys Lys
805 810 815

Gly Arg Phe Leu Ser Lys Glu Glu Arg Ala Glu Glu Trp Glu Arg Gly
820 825 830

Lys Glu Arg Phe Arg Asp Leu Glu Ala Trp Ser Tyr Ser Ala Ala Arg
835 840 845

Arg Ile Glu Asp Ala Phe Ala Gly Ile Glu Tyr Ala Ser Pro Gly Asn
850 855 860

Lys Lys Lys Ile Glu Gln Leu Leu Arg Asp Leu Ser Leu Trp Glu Ala
865 870 875 880

Phe Glu Ser Lys Leu Lys Val Arg Ala Asp Arg Ile Asn Leu Ala Lys
885 890 895

Leu Lys Lys Glu Ile Leu Glu Ala Gln Glu His Pro Tyr His Asp Phe
900 905 910

Lys Ser Trp Gln Lys Phe Glu Arg Glu Leu Arg Leu Val Lys Asn Gln
915 920 925

Asp Ile Ile Thr Trp Met Met Cys Arg Asp Leu Met Glu Glu Asn Lys
930 935 940

Val Glu Gly Leu Asp Thr Gly Thr Leu Tyr Leu Lys Asp Ile Arg Pro
945 950 955 960

Asn Val Gln Glu Gln Gly Ser Leu Asn Val Leu Asn Arg Val Lys Pro
965 970 975

Met Arg Leu Pro Val Val Val Tyr Arg Ala Asp Ser Arg Gly His Val
980 985 990

His Lys Glu Glu Ala Pro Leu Ala Thr Val Tyr Ile Glu Glu Arg Asp
995 1000 1005

Thr Lys Leu Leu Lys Gln Gly Asn Phe Lys Ser Phe Val Lys Asp
1010 1015 1020

Arg Arg Leu Asn Gly Leu Phe Ser Phe Val Asp Thr Gly Gly Leu
1025 1030 1035

Ala Met Glu Gln Tyr Pro Ile Ser Lys Leu Arg Val Glu Tyr Glu
1040 1045 1050

Leu Ala Lys Tyr Gln Thr Ala Arg Val Cys Val Phe Glu Leu Thr
1055 1060 1065

Leu Arg Leu Glu Glu Ser Leu Leu Thr Arg Tyr Pro His Leu Pro
1070 1075 1080

Asp Glu Ser Phe Arg Glu Met Leu Glu Ser Trp Ser Asp Pro Leu
1085 1090 1095

Leu Ala Lys Trp Pro Glu Leu His Gly Lys Val Arg Leu Leu Ile
1100 1105 1110

Ala Val Arg Asn Ala Phe Ser His Asn Gln Tyr Pro Met Tyr Asp
1115 1120 1125

Glu Ala Val Phe Ser Ser Ile Arg Lys Tyr Asp Pro Ser Ser Pro
1130 1135 1140

Asp Ala Ile Glu Glu Arg Met Gly Leu Asn Ile Ala His Arg Leu
1145 1150 1155

Ser Glu Glu Val Lys Gln Ala Lys Glu Thr Val Glu Arg Ile Ile
1160 1165 1170

Gln Ala Gly Ser Leu Gln
1175

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<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> PguCas13b direct repeat

<400> 64
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<210> 65
<211> 2943
<212> DNA
<213> Artificial Sequence

<220>
<223> RfxCas13d-SV40NLS nucleic acid sequence

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gccgaaggca gcgacgccag gctggaaaag atcgtggagg gcgacagcat caggagcgtg 180
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gaaaaaatcc tcgccgaata cattaccaac gccgcctacg cgtcaacaa tatctccggc 480
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aacgcctacc tgaggaacac caagtggaat gtgatcatca gggaggacct cctgagaatt 2580
gacaacaaga catgtaccct gttcgcaaac aaggccgtcg ccctggaagt ggccagggtat 2640
gtccacgcct atatcaacga cattgccgag gtcaattcct acttccaact gtaccattac 2700
atcatgcaga gaattatcat gaatgagagg tacgagaaaa gcagcggaaa ggtgtccgag 2760
tacttcgacg ctgtgaatga cgagaagaag tacaacgata ggctcctgaa actgctgtgt 2820
gtgcctttcg gctactgtat ccccaggttt aagaacctga gcatcgaggc cctgttcgat 2880
aggaacgagg ccgccaagtt cgacaaggag aaaaagaagg tgtccggcaa ttccggatcc 2940
gga 2943

<210> 66
<211> 981
<212> PRT
<213> Artificial Sequence

<220>
<223> RfxCas13d-SV40NLS amino acid sequence

<400> 66

Met Ser Pro Lys Lys Lys Arg Lys Val Glu Ala Ser Ile Glu Lys Lys
1 5 10 15

Lys Ser Phe Ala Lys Gly Met Gly Val Lys Ser Thr Leu Val Ser Gly
20 25 30

Ser Lys Val Tyr Met Thr Thr Phe Ala Glu Gly Ser Asp Ala Arg Leu
35 40 45

Glu Lys Ile Val Glu Gly Asp Ser Ile Arg Ser Val Asn Glu Gly Glu
50 55 60

Ala Phe Ser Ala Glu Met Ala Asp Lys Asn Ala Gly Tyr Lys Ile Gly
65 70 75 80

Asn Ala Lys Phe Ser His Pro Lys Gly Tyr Ala Val Val Ala Asn Asn
85 90 95

Pro Leu Tyr Thr Gly Pro Val Gln Gln Asp Met Leu Gly Leu Lys Glu
100 105 110

Thr Leu Glu Lys Arg Tyr Phe Gly Glu Ser Ala Asp Gly Asn Asp Asn
115 120 125

Ile Cys Ile Gln Val Ile His Asn Ile Leu Asp Ile Glu Lys Ile Leu
130 135 140

Ala Glu Tyr Ile Thr Asn Ala Ala Tyr Ala Val Asn Asn Ile Ser Gly
145 150 155 160

Leu Asp Lys Asp Ile Ile Gly Phe Gly Lys Phe Ser Thr Val Tyr Thr
165 170 175

Tyr Asp Glu Phe Lys Asp Pro Glu His His Arg Ala Ala Phe Asn Asn
180 185 190

Asn Asp Lys Leu Ile Asn Ala Ile Lys Ala Gln Tyr Asp Glu Phe Asp
195 200 205

Asn Phe Leu Asp Asn Pro Arg Leu Gly Tyr Phe Gly Gln Ala Phe Phe
210 215 220

Ser Lys Glu Gly Arg Asn Tyr Ile Ile Asn Tyr Gly Asn Glu Cys Tyr
225 230 235 240

Asp Ile Leu Ala Leu Leu Ser Gly Leu Ala His Trp Val Val Ala Asn
245 250 255

Asn Glu Glu Glu Ser Arg Ile Ser Arg Thr Trp Leu Tyr Asn Leu Asp
260 265 270

Lys Asn Leu Asp Asn Glu Tyr Ile Ser Thr Leu Asn Tyr Leu Tyr Asp
275 280 285

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

Asn Val Asn Tyr Ile Ala Glu Thr Leu Gly Ile Asn Pro Ala Glu Phe
305 310 315 320

Ala Glu Gln Tyr Phe Arg Phe Ser Ile Met Lys Glu Gln Lys Asn Leu
325 330 335

Gly Phe Asn Ile Thr Lys Leu Arg Glu Val Met Leu Asp Arg Lys Asp
340 345 350

Met Ser Glu Ile Arg Lys Asn His Lys Val Phe Asp Ser Ile Arg Thr
355 360 365

Lys Val Tyr Thr Met Met Asp Phe Val Ile Tyr Arg Tyr Tyr Ile Glu
370 375 380

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

Lys Ser Leu Ser Glu Lys Asp Ile Phe Val Ile Asn Leu Arg Gly Ser
405 410 415

Phe Asn Asp Asp Gln Lys Asp Ala Leu Tyr Tyr Asp Glu Ala Asn Arg
420 425 430

Ile Trp Arg Lys Leu Glu Asn Ile Met His Asn Ile Lys Glu Phe Arg
435 440 445

Gly Asn Lys Thr Arg Glu Tyr Lys Lys Lys Asp Ala Pro Arg Leu Pro
450 455 460

Arg Ile Leu Pro Ala Gly Arg Asp Val Ser Ala Phe Ser Lys Leu Met
465 470 475 480

Tyr Ala Leu Thr Met Phe Leu Asp Gly Lys Glu Ile Asn Asp Leu Leu
485 490 495

Thr Thr Leu Ile Asn Lys Phe Asp Asn Ile Gln Ser Phe Leu Lys Val
500 505 510

Met Pro Leu Ile Gly Val Asn Ala Lys Phe Val Glu Glu Tyr Ala Phe
515 520 525

Phe Lys Asp Ser Ala Lys Ile Ala Asp Glu Leu Arg Leu Ile Lys Ser
530 535 540

Phe Ala Arg Met Gly Glu Pro Ile Ala Asp Ala Arg Arg Ala Met Tyr
545 550 555 560

Ile Asp Ala Ile Arg Ile Leu Gly Thr Asn Leu Ser Tyr Asp Glu Leu
565 570 575

Lys Ala Leu Ala Asp Thr Phe Ser Leu Asp Glu Asn Gly Asn Lys Leu
580 585 590

Lys Lys Gly Lys His Gly Met Arg Asn Phe Ile Ile Asn Asn Val Ile
595 600 605

Ser Asn Lys Arg Phe His Tyr Leu Ile Arg Tyr Gly Asp Pro Ala His
610 615 620

Leu His Glu Ile Ala Lys Asn Glu Ala Val Val Lys Phe Val Leu Gly
625 630 635 640

Arg Ile Ala Asp Ile Gln Lys Lys Gln Gly Gln Asn Gly Lys Asn Gln
645 650 655

Ile Asp Arg Tyr Tyr Glu Thr Cys Ile Gly Lys Asp Lys Gly Lys Ser
660 665 670

Val Ser Glu Lys Val Asp Ala Leu Thr Lys Ile Ile Thr Gly Met Asn
675 680 685

Tyr Asp Gln Phe Asp Lys Lys Arg Ser Val Ile Glu Asp Thr Gly Arg
690 695 700

Glu Asn Ala Glu Arg Glu Lys Phe Lys Lys Ile Ile Ser Leu Tyr Leu
705 710 715 720

Thr Val Ile Tyr His Ile Leu Lys Asn Ile Val Asn Ile Asn Ala Arg
725 730 735

Tyr Val Ile Gly Phe His Cys Val Glu Arg Asp Ala Gln Leu Tyr Lys
740 745 750

Glu Lys Gly Tyr Asp Ile Asn Leu Lys Lys Leu Glu Glu Lys Gly Phe
755 760 765

Ser Ser Val Thr Lys Leu Cys Ala Gly Ile Asp Glu Thr Ala Pro Asp
770 775 780

Lys Arg Lys Asp Val Glu Lys Glu Met Ala Glu Arg Ala Lys Glu Ser
785 790 795 800

Ile Asp Ser Leu Glu Ser Ala Asn Pro Lys Leu Tyr Ala Asn Tyr Ile
805 810 815

Lys Tyr Ser Asp Glu Lys Lys Ala Glu Glu Phe Thr Arg Gln Ile Asn
820 825 830

Arg Glu Lys Ala Lys Thr Ala Leu Asn Ala Tyr Leu Arg Asn Thr Lys
835 840 845

Trp Asn Val Ile Ile Arg Glu Asp Leu Leu Arg Ile Asp Asn Lys Thr
850 855 860

Cys Thr Leu Phe Ala Asn Lys Ala Val Ala Leu Glu Val Ala Arg Tyr
865 870 875 880

Val His Ala Tyr Ile Asn Asp Ile Ala Glu Val Asn Ser Tyr Phe Gln
885 890 895

Leu Tyr His Tyr Ile Met Gln Arg Ile Ile Met Asn Glu Arg Tyr Glu
900 905 910

Lys Ser Ser Gly Lys Val Ser Glu Tyr Phe Asp Ala Val Asn Asp Glu
915 920 925

Lys Lys Tyr Asn Asp Arg Leu Leu Lys Leu Leu Cys Val Pro Phe Gly
930 935 940

Tyr Cys Ile Pro Arg Phe Lys Asn Leu Ser Ile Glu Ala Leu Phe Asp
945 950 955 960

Arg Asn Glu Ala Ala Lys Phe Asp Lys Glu Lys Lys Lys Val Ser Gly
965 970 975

Asn Ser Gly Ser Gly
980

<210> 67
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> RfxCas13d direct repeat

<400> 67
aaccctacc aactggtcgg ggtttgaaac 30

<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> SV40 Nuclear Localization Signaling nucleic acid sequence

<400> 68
ccaaagaaga agcggaaggt cggt 24

<210> 69
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> SV40 Nuclear Localization Signaling amino acid sequence

<400> 69

Pro Lys Lys Lys Arg Lys Val
1 5

<210> 70
<211> 1479
<212> DNA
<213> Artificial Sequence

<220>
<223> CMV-BD-2xms2-PPT-exon-bGHpA repair template

<400> 70

tagttattaa tagtaatcaa ttacgggggtc attagttcat agcccatata tggagttccg	60
cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc cccgcccatt	120
gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca	180
atgggtggag tattttacggt aaactgccc cttggcagta catcaagtgt atcatatgcc	240
aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta	300
catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac	360
catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg	420
atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg	480
ggactttcca aaatgtcgt acaactccgc ccattgacg caaatgggcg gtaggcgtgt	540
acggtgggag gtctatataa gcagagctgg tttagtgaac cgtcggatct tccatttcgg	600
gtgtcgtgac gtacgaatac gatctagacc ctgcatcctc tctgggacac tcaacaccct	660
cacggacagc ccgaattcga cccaagctga cgggagcaca tgaggatcac ccatgtgcca	720
cgagcgacat gaggatcacc catgtcgctt tcactagtct gtggtgtgat atccatggcg	780
gcctacttat cctgtccctt ttttttccac aggagcgcac catcttcttc aaggacgacg	840
gcaactacaa gaccgcgcc gaggtgaagt tcgagggcga caccctggtg aaccgcatcg	900
agctgaaggg catcgacttc aaggaggacg gcaacatcct ggggcacaag ctggagtaca	960
actacaacag ccacaacgtc tatatcatgg ccgacaagca gaagaacggc atcaaggtga	1020
acttcaagat ccgccacaac atcgaggacg gcagcgtgca gctcgccgac cactaccagc	1080
agaacacccc catcggcgac ggccccgtgc tgctgcccga caaccactac ctgagcacc	1140
agtccgccct gagcaaagac cccaacgaga agcgcgatca catggtcctg ctggagttcg	1200
tgaccgccgc cgggatcact ctcggcatgg acgagctgta caagtaacta gagctcgctg	1260
atcagcctcg actgtgcctt ctagttgcca gccatctgtt gtttgcccct cccccgtgcc	1320
ttccttgacc ctggaaggtg ccactccac tgtcctttcc taataaaatg aggaaattgc	1380
atcgcatgtg ctgagtaggt gtcattctat tctggggggg ggggtggggc aggacagcaa	1440
gggggaggat tgggaagaga atagcaggca tgctgggga	1479

<210> 71

<211> 3357

<212> DNA
<213> Artificial Sequence

<220>
<223> PinCas13b nucleic acid sequence

<400> 71
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gacagacagc tggcctacag caaggccgac atcaccaacg acgaggacat cctgttcttc 180
aaaggccagt ggaagaacct ggacaacgac ctggaacgga aggccagact gagaagcctg 240
atcctgaagc acttcagctt tctggaaggc gccgcttacg gcaagaagct gtttgagtct 300
cagagcagcg gcaacaagag cagcaagaag aaagagctgt ccaagaaaga gaaagaggaa 360
ctgcaggcca acgctctgag cctggacaat ctgaagtcta tcctgttcga cttcctgcag 420
aagctgaagg acttccggaa ctactacagc cactacagac accccgagag cagcgagctg 480
cctctgttcg atggcaacat gctgcagcgg ctgtacaacg tgctcgacgt gtccgtgcag 540
cgcgtgaaga gagatcacga gcacaacgac aagggtggacc ctcaccggca cttcaatcac 600
ctcgtgcgga agggcaagaa ggataagtac ggcaacaacg ataaccggtt cttcaagcac 660
cacttcgtgg accgcgaggg cacagtgaca gaagccggac tgctgttctt cgtgtccctg 720
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cctcactacc acatcgagaa gggaaagatc ggcctgagat tcgtgcccga gggacagcat 1380
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gctctgtttg	gaggcgagaa	agagaggctg	acccatact	tccggcagat	gaatctgacc	2040
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ctgtccttct	accggtccta	cctggaagcc	cgggaaggctt	tcctgcagtc	catcggcaga	2160
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tccaaagaga	agcgggcca	agagtgggag	agcggcaaag	agagattccg	gctggccaag	2520
ctgaagaaa	aaatcctcga	agccaaagag	caccctacc	acgacttcaa	gagctggcag	2580
aagttcgagc	gcgagctgag	actggtcaag	aaccaggaca	tcatcacctg	gatgatgtgc	2640
cgggacctga	tggaagaaaa	caaagtggaa	ggcctggata	caggcaccct	gtacctgaag	2700
gacatcagga	ccgacgtgca	agagcagggc	agcctgaacg	tgctgaacag	agtgaagccc	2760
atgagactgc	ccgtggtggt	gtacagagcc	gatagcagag	gccacgtgca	caaagaacag	2820
gcccctctgg	ccaccgtgta	catcgaggaa	agagacacca	agctgctgaa	gcagggcaac	2880
ttcaagtcct	tcgtgaagga	cagacggctg	aatggcctgt	tcagcttcgt	ggatactggc	2940
gccctggcca	tggaacagta	ccccatctct	aaactgcgcg	tggaatacga	gctggccaaa	3000
taccagaccg	ccagagtgtg	cgccttcgag	cagacactgg	aactggaaga	gagcctgctg	3060

acccggtatc ctcattctgcc cgacaagaac tttcggaaga tgctcgaatc ttggagcgac 3120
 cctctgctgg ataagtggcc tgacctgcac ggaaatgtgc ggctgctgat cgccgtgcgg 3180
 aatgccttta gccacaatca gtaccctatg tacgacgaga cactgttttag ctccatccgg 3240
 aagtacgacc ctagcagccc tgacgccatt gaggaacgga tgggcctgaa tatcgccac 3300
 agactgtctg aggaagtgaa gcaggccaaa gaaatggtgg aacggatcat tcaggcc 3357

<210> 72
 <211> 1119
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PinCas13b amino acid sequence

<400> 72

Met Thr Glu Gln Asn Glu Lys Pro Tyr Asn Gly Thr Tyr Tyr Thr Leu
 1 5 10 15

Glu Asp Lys His Phe Trp Ala Ala Phe Leu Asn Leu Ala Arg His Asn
 20 25 30

Ala Tyr Ile Thr Leu Ala His Ile Asp Arg Gln Leu Ala Tyr Ser Lys
 35 40 45

Ala Asp Ile Thr Asn Asp Glu Asp Ile Leu Phe Phe Lys Gly Gln Trp
 50 55 60

Lys Asn Leu Asp Asn Asp Leu Glu Arg Lys Ala Arg Leu Arg Ser Leu
 65 70 75 80

Ile Leu Lys His Phe Ser Phe Leu Glu Gly Ala Ala Tyr Gly Lys Lys
 85 90 95

Leu Phe Glu Ser Gln Ser Ser Gly Asn Lys Ser Ser Lys Lys Lys Glu
 100 105 110

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

Asp Asn Leu Lys Ser Ile Leu Phe Asp Phe Leu Gln Lys Leu Lys Asp
130 135 140

Phe Arg Asn Tyr Tyr Ser His Tyr Arg His Pro Glu Ser Ser Glu Leu
145 150 155 160

Pro Leu Phe Asp Gly Asn Met Leu Gln Arg Leu Tyr Asn Val Phe Asp
165 170 175

Val Ser Val Gln Arg Val Lys Arg Asp His Glu His Asn Asp Lys Val
180 185 190

Asp Pro His Arg His Phe Asn His Leu Val Arg Lys Gly Lys Lys Asp
195 200 205

Lys Tyr Gly Asn Asn Asp Asn Pro Phe Phe Lys His His Phe Val Asp
210 215 220

Arg Glu Gly Thr Val Thr Glu Ala Gly Leu Leu Phe Phe Val Ser Leu
225 230 235 240

Phe Leu Glu Lys Arg Asp Ala Ile Trp Met Gln Lys Lys Ile Arg Gly
245 250 255

Phe Lys Gly Gly Thr Glu Ala Tyr Gln Gln Met Thr Asn Glu Val Phe
260 265 270

Cys Arg Ser Arg Ile Ser Leu Pro Lys Leu Lys Leu Glu Ser Leu Arg
275 280 285

Thr Asp Asp Trp Met Leu Leu Asp Met Leu Asn Glu Leu Val Arg Cys
290 295 300

His Lys Ser Leu Tyr Asp Arg Leu Arg Glu Glu Asp Arg Ala Arg Phe
305 310 315 320

Arg Val Pro Val Asp Ile Leu Ser Asp Glu Asp Asp Thr Asp Gly Thr
325 330 335

Glu Glu Asp Pro Phe Lys Asn Thr Leu Val Arg His Gln Asp Arg Phe
340 345 350

Pro Tyr Phe Ala Leu Arg Tyr Phe Asp Leu Lys Lys Val Phe Thr Ser
355 360 365

Leu Arg Phe His Ile Asp Leu Gly Thr Tyr His Phe Ala Ile Tyr Lys
370 375 380

Lys Asn Ile Gly Glu Gln Pro Glu Asp Arg His Leu Thr Arg Asn Leu
385 390 395 400

Tyr Gly Phe Gly Arg Ile Gln Asp Phe Ala Glu Glu His Arg Pro Glu
405 410 415

Glu Trp Lys Arg Leu Val Arg Asp Leu Asp Tyr Phe Glu Thr Gly Asp
420 425 430

Lys Pro Tyr Ile Thr Gln Thr Thr Pro His Tyr His Ile Glu Lys Gly
435 440 445

Lys Ile Gly Leu Arg Phe Val Pro Glu Gly Gln His Leu Trp Pro Ser
450 455 460

Pro Glu Val Gly Ala Thr Arg Thr Gly Arg Ser Lys Tyr Ala Gln Asp
465 470 475 480

Lys Arg Leu Thr Ala Glu Ala Phe Leu Ser Val His Glu Leu Met Pro
485 490 495

Met Met Phe Tyr Tyr Phe Leu Leu Arg Glu Lys Tyr Ser Glu Glu Val
500 505 510

Ser Ala Glu Lys Val Gln Gly Arg Ile Lys Arg Val Ile Glu Asp Val
515 520 525

Tyr Ala Val Tyr Asp Ala Phe Ala Arg Asp Glu Ile Asn Thr Arg Asp
530 535 540

Glu Leu Asp Ala Cys Leu Ala Asp Lys Gly Ile Arg Arg Gly His Leu
545 550 555 560

Pro Arg Gln Met Ile Ala Ile Leu Ser Gln Glu His Lys Asp Met Glu
565 570 575

Glu Lys Val Arg Lys Lys Leu Gln Glu Met Ile Ala Asp Thr Asp His
580 585 590

Arg Leu Asp Met Leu Asp Arg Gln Thr Asp Arg Lys Ile Arg Ile Gly
595 600 605

Arg Lys Asn Ala Gly Leu Pro Lys Ser Gly Val Val Ala Asp Trp Leu
610 615 620

Val Arg Asp Met Met Arg Phe Gln Pro Val Ala Lys Asp Thr Ser Gly
625 630 635 640

Lys Pro Leu Asn Asn Ser Lys Ala Asn Ser Thr Glu Tyr Arg Met Leu
645 650 655

Gln Arg Ala Leu Ala Leu Phe Gly Gly Glu Lys Glu Arg Leu Thr Pro
660 665 670

Tyr Phe Arg Gln Met Asn Leu Thr Gly Gly Asn Asn Pro His Pro Phe
675 680 685

Leu His Glu Thr Arg Trp Glu Ser His Thr Asn Ile Leu Ser Phe Tyr
690 695 700

Arg Ser Tyr Leu Glu Ala Arg Lys Ala Phe Leu Gln Ser Ile Gly Arg
705 710 715 720

Ser Asp Arg Val Glu Asn His Arg Phe Leu Leu Leu Lys Glu Pro Lys
725 730 735

Thr Asp Arg Gln Thr Leu Val Ala Gly Trp Lys Gly Glu Phe His Leu
740 745 750

Pro Arg Gly Ile Phe Thr Glu Ala Val Arg Asp Cys Leu Ile Glu Met
755 760 765

Gly Tyr Asp Glu Val Gly Ser Tyr Lys Glu Val Gly Phe Met Ala Lys
770 775 780

Ala Val Pro Leu Tyr Phe Glu Arg Ala Ser Lys Asp Arg Val Gln Pro
785 790 795 800

Phe Tyr Asp Tyr Pro Phe Asn Val Gly Asn Ser Leu Lys Pro Lys Lys
805 810 815

Gly Arg Phe Leu Ser Lys Glu Lys Arg Ala Glu Glu Trp Glu Ser Gly
820 825 830

Lys Glu Arg Phe Arg Leu Ala Lys Leu Lys Lys Glu Ile Leu Glu Ala
835 840 845

Lys Glu His Pro Tyr His Asp Phe Lys Ser Trp Gln Lys Phe Glu Arg
850 855 860

Glu Leu Arg Leu Val Lys Asn Gln Asp Ile Ile Thr Trp Met Met Cys
865 870 875 880

Arg Asp Leu Met Glu Glu Asn Lys Val Glu Gly Leu Asp Thr Gly Thr
885 890 895

Leu Tyr Leu Lys Asp Ile Arg Thr Asp Val Gln Glu Gln Gly Ser Leu
900 905 910

Asn Val Leu Asn Arg Val Lys Pro Met Arg Leu Pro Val Val Val Tyr
915 920 925

Arg Ala Asp Ser Arg Gly His Val His Lys Glu Gln Ala Pro Leu Ala
930 935 940

Thr Val Tyr Ile Glu Glu Arg Asp Thr Lys Leu Leu Lys Gln Gly Asn
945 950 955 960

Phe Lys Ser Phe Val Lys Asp Arg Arg Leu Asn Gly Leu Phe Ser Phe
965 970 975

Val Asp Thr Gly Ala Leu Ala Met Glu Gln Tyr Pro Ile Ser Lys Leu
980 985 990

Arg Val Glu Tyr Glu Leu Ala Lys Tyr Gln Thr Ala Arg Val Cys Ala
 995 1000 1005

Phe Glu Gln Thr Leu Glu Leu Glu Glu Ser Leu Leu Thr Arg Tyr
 1010 1015 1020

Pro His Leu Pro Asp Lys Asn Phe Arg Lys Met Leu Glu Ser Trp
 1025 1030 1035

Ser Asp Pro Leu Leu Asp Lys Trp Pro Asp Leu His Gly Asn Val
 1040 1045 1050

Arg Leu Leu Ile Ala Val Arg Asn Ala Phe Ser His Asn Gln Tyr
 1055 1060 1065

Pro Met Tyr Asp Glu Thr Leu Phe Ser Ser Ile Arg Lys Tyr Asp
 1070 1075 1080

Pro Ser Ser Pro Asp Ala Ile Glu Glu Arg Met Gly Leu Asn Ile
 1085 1090 1095

Ala His Arg Leu Ser Glu Glu Val Lys Gln Ala Lys Glu Met Val
 1100 1105 1110

Glu Arg Ile Ile Gln Ala
 1115

<210> 73
 <211> 36
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PinCas13b direct repeat

<400> 73
 gttgcatctg cctgctgttt gcaaggtaaa aacaac

36

<210> 74
 <211> 3579
 <212> DNA
 <213> Artificial Sequence

<220>

<223> BzoCas13b nucleic acid sequence

<400> 74

atggagaata ccgactccgt gttccgggag ctgggcaaga gactgaaggg caaggagtac	60
acatctgaga acttctttga cgccatcttt aaggagaata tctctctggt ggagtacgag	120
cggtatgtga agctgctgag cgattatttc cccatggccc ggctgctgga caagaaggag	180
gtgcctatca aggagagaaa ggagaacttc aagaagaact tcaaggcat catcaaggcc	240
gtgcgggatc tgagaaactt ttacaccac aaggagcacg gcgaggtgga gatcacagac	300
gagatcttcg gcgtgctgga tgagatgctg aagtccaccg tgctgacagt gaagaagaag	360
aagtgaaaa ccgacaagac aaaggagatc ctgaagaagt ctatcgagaa gcagctggat	420
atcctgtgcc agaagaagct ggagtacctg aggacaccg cccgcaagat cgaggagaag	480
cggagaaacc agaggagag gggagagaag gagctggtgg caccttttaa gtattctgat	540
aagcgggacg acctgatcgc cgccatctac aatgacgcct tcgacgtgta tatcgacaag	600
aagaaggatt ccctgaagga gagctccaag gccaaagtaca acacaaagtc tgaccctcag	660
caggaggagg gcgatctgaa gatcccaatc agcaagaatg gcgtggtgtt cctgctgtcc	720
ctgtttctga ccaagcagga gatccacgcc ttcaagagca agatcgccgg cttaaggcc	780
acagtgatcg acgaggccac cgtgtccgag gccacagtgt ctcacggcaa gaacagcatc	840
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ctgaaggatg agcagaccgt gagggagaag gagtacaatg acttcatcgc ctatcaggat	2040
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gagaattacc cctatgtggt ggagagagag atcgagcagt acgagaaggt gcggagagag	3180

gagctgctga aggaggtgca cctgatcgag gagtatatcc tggagaaggt gaaggataaa 3240
gaaatcctga agaagggcga caaccagaac ttcaagtact atatcctgaa cggcctgctg 3300
aagcagctga agaatgagga tgtggagtcc tacaagggtgt tcaacctgaa taccgagcca 3360
gaggatgtga acatcaatca gctgaagcag gaggccaccg acctggagca gaaggccttc 3420
gtgctgacat atatccggaa caagtttgcc cacaatcagc tgcccaagaa ggagttctgg 3480
gactactgtc aggagaagta tggcaagatc gagaaggaga aaacctacgc cgagtatttc 3540
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<210> 75
<211> 1193
<212> PRT
<213> Artificial Sequence

<220>
<223> BzoCas13b amino acid sequence

<400> 75

Met Glu Asn Thr Asp Ser Val Phe Arg Glu Leu Gly Lys Arg Leu Lys
1 5 10 15

Gly Lys Glu Tyr Thr Ser Glu Asn Phe Phe Asp Ala Ile Phe Lys Glu
20 25 30

Asn Ile Ser Leu Val Glu Tyr Glu Arg Tyr Val Lys Leu Leu Ser Asp
35 40 45

Tyr Phe Pro Met Ala Arg Leu Leu Asp Lys Lys Glu Val Pro Ile Lys
50 55 60

Glu Arg Lys Glu Asn Phe Lys Lys Asn Phe Lys Gly Ile Ile Lys Ala
65 70 75 80

Val Arg Asp Leu Arg Asn Phe Tyr Thr His Lys Glu His Gly Glu Val
85 90 95

Glu Ile Thr Asp Glu Ile Phe Gly Val Leu Asp Glu Met Leu Lys Ser
100 105 110

Thr Val Leu Thr Val Lys Lys Lys Lys Val Lys Thr Asp Lys Thr Lys
115 120 125

Glu Ile Leu Lys Lys Ser Ile Glu Lys Gln Leu Asp Ile Leu Cys Gln
130 135 140

Lys Lys Leu Glu Tyr Leu Arg Asp Thr Ala Arg Lys Ile Glu Glu Lys
145 150 155 160

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

Lys Tyr Ser Asp Lys Arg Asp Asp Leu Ile Ala Ala Ile Tyr Asn Asp
180 185 190

Ala Phe Asp Val Tyr Ile Asp Lys Lys Lys Asp Ser Leu Lys Glu Ser
195 200 205

Ser Lys Ala Lys Tyr Asn Thr Lys Ser Asp Pro Gln Gln Glu Glu Gly
210 215 220

Asp Leu Lys Ile Pro Ile Ser Lys Asn Gly Val Val Phe Leu Leu Ser
225 230 235 240

Leu Phe Leu Thr Lys Gln Glu Ile His Ala Phe Lys Ser Lys Ile Ala
245 250 255

Gly Phe Lys Ala Thr Val Ile Asp Glu Ala Thr Val Ser Glu Ala Thr
260 265 270

Val Ser His Gly Lys Asn Ser Ile Cys Phe Met Ala Thr His Glu Ile
275 280 285

Phe Ser His Leu Ala Tyr Lys Lys Leu Lys Arg Lys Val Arg Thr Ala
290 295 300

Glu Ile Asn Tyr Gly Glu Ala Glu Asn Ala Glu Gln Leu Ser Val Tyr
305 310 315 320

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

Pro Asp Val Val Tyr Gln Asn Leu Ser Glu Asp Val Gln Lys Thr Phe
340 345 350

Ile Glu Asp Trp Asn Glu Tyr Leu Lys Glu Asn Asn Gly Asp Val Gly
355 360 365

Thr Met Glu Glu Glu Gln Val Ile His Pro Val Ile Arg Lys Arg Tyr
370 375 380

Glu Asp Lys Phe Asn Tyr Phe Ala Ile Arg Phe Leu Asp Glu Phe Ala
385 390 395 400

Gln Phe Pro Thr Leu Arg Phe Gln Val His Leu Gly Asn Tyr Leu His
405 410 415

Asp Ser Arg Pro Lys Glu Asn Leu Ile Ser Asp Arg Arg Ile Lys Glu
420 425 430

Lys Ile Thr Val Phe Gly Arg Leu Ser Glu Leu Glu His Lys Lys Ala
435 440 445

Leu Phe Ile Lys Asn Thr Glu Thr Asn Glu Asp Arg Glu His Tyr Trp
450 455 460

Glu Ile Phe Pro Asn Pro Asn Tyr Asp Phe Pro Lys Glu Asn Ile Ser
465 470 475 480

Val Asn Asp Lys Asp Phe Pro Ile Ala Gly Ser Ile Leu Asp Arg Glu
485 490 495

Lys Gln Pro Val Ala Gly Lys Ile Gly Ile Lys Val Lys Leu Leu Asn
500 505 510

Gln Gln Tyr Val Ser Glu Val Asp Lys Ala Val Lys Ala His Gln Leu
515 520 525

Lys Gln Arg Lys Ala Ser Lys Pro Ser Ile Gln Asn Ile Ile Glu Glu
530 535 540

Ile Val Pro Ile Asn Glu Ser Asn Pro Lys Glu Ala Ile Val Phe Gly
545 550 555 560

Gly Gln Pro Thr Ala Tyr Leu Ser Met Asn Asp Ile His Ser Ile Leu
565 570 575

Tyr Glu Phe Phe Asp Lys Trp Glu Lys Lys Lys Glu Lys Leu Glu Lys
580 585 590

Lys Gly Glu Lys Glu Leu Arg Lys Glu Ile Gly Lys Glu Leu Glu Lys
595 600 605

Lys Ile Val Gly Lys Ile Gln Ala Gln Ile Gln Gln Ile Ile Asp Lys
610 615 620

Asp Thr Asn Ala Lys Ile Leu Lys Pro Tyr Gln Asp Gly Asn Ser Thr
625 630 635 640

Ala Ile Asp Lys Glu Lys Leu Ile Lys Asp Leu Lys Gln Glu Gln Asn
645 650 655

Ile Leu Gln Lys Leu Lys Asp Glu Gln Thr Val Arg Glu Lys Glu Tyr
660 665 670

Asn Asp Phe Ile Ala Tyr Gln Asp Lys Asn Arg Glu Ile Asn Lys Val
675 680 685

Arg Asp Arg Asn His Lys Gln Tyr Leu Lys Asp Asn Leu Lys Arg Lys
690 695 700

Tyr Pro Glu Ala Pro Ala Arg Lys Glu Val Leu Tyr Tyr Arg Glu Lys
705 710 715 720

Gly Lys Val Ala Val Trp Leu Ala Asn Asp Ile Lys Arg Phe Met Pro
725 730 735

Thr Asp Phe Lys Asn Glu Trp Lys Gly Glu Gln His Ser Leu Leu Gln
740 745 750

Lys Ser Leu Ala Tyr Tyr Glu Gln Cys Lys Glu Glu Leu Lys Asn Leu
755 760 765

Leu Pro Glu Lys Val Phe Gln His Leu Pro Phe Lys Leu Gly Gly Tyr
770 775 780

Phe Gln Gln Lys Tyr Leu Tyr Gln Phe Tyr Thr Cys Tyr Leu Asp Lys
785 790 795 800

Arg Leu Glu Tyr Ile Ser Gly Leu Val Gln Gln Ala Glu Asn Phe Lys
805 810 815

Ser Glu Asn Lys Val Phe Lys Lys Val Glu Asn Glu Cys Phe Lys Phe
820 825 830

Leu Lys Lys Gln Asn Tyr Thr His Lys Glu Leu Asp Ala Arg Val Gln
835 840 845

Ser Ile Leu Gly Tyr Pro Ile Phe Leu Glu Arg Gly Phe Met Asp Glu
850 855 860

Lys Pro Thr Ile Ile Lys Gly Lys Thr Phe Lys Gly Asn Glu Ala Leu
865 870 875 880

Phe Ala Asp Trp Phe Arg Tyr Tyr Lys Glu Tyr Gln Asn Phe Gln Thr
885 890 895

Phe Tyr Asp Thr Glu Asn Tyr Pro Leu Val Glu Leu Glu Lys Lys Gln
900 905 910

Ala Asp Arg Lys Arg Lys Thr Lys Ile Tyr Gln Gln Lys Lys Asn Asp
915 920 925

Val Phe Thr Leu Leu Met Ala Lys His Ile Phe Lys Ser Val Phe Lys
930 935 940

Gln Asp Ser Ile Asp Gln Phe Ser Leu Glu Asp Leu Tyr Gln Ser Arg
945 950 955 960

Glu Glu Arg Leu Gly Asn Gln Glu Arg Ala Arg Gln Thr Gly Glu Arg
965 970 975

Asn Thr Asn Tyr Ile Trp Asn Lys Thr Val Asp Leu Lys Leu Cys Asp
980 985 990

Gly Lys Ile Thr Val Glu Asn Val Lys Leu Lys Asn Val Gly Asp Phe
995 1000 1005

Ile Lys Tyr Glu Tyr Asp Gln Arg Val Gln Ala Phe Leu Lys Tyr
1010 1015 1020

Glu Glu Asn Ile Glu Trp Gln Ala Phe Leu Ile Lys Glu Ser Lys
1025 1030 1035

Glu Glu Glu Asn Tyr Pro Tyr Val Val Glu Arg Glu Ile Glu Gln
1040 1045 1050

Tyr Glu Lys Val Arg Arg Glu Glu Leu Leu Lys Glu Val His Leu
1055 1060 1065

Ile Glu Glu Tyr Ile Leu Glu Lys Val Lys Asp Lys Glu Ile Leu
1070 1075 1080

Lys Lys Gly Asp Asn Gln Asn Phe Lys Tyr Tyr Ile Leu Asn Gly
1085 1090 1095

Leu Leu Lys Gln Leu Lys Asn Glu Asp Val Glu Ser Tyr Lys Val
1100 1105 1110

Phe Asn Leu Asn Thr Glu Pro Glu Asp Val Asn Ile Asn Gln Leu
1115 1120 1125

Lys Gln Glu Ala Thr Asp Leu Glu Gln Lys Ala Phe Val Leu Thr
1130 1135 1140

Tyr Ile Arg Asn Lys Phe Ala His Asn Gln Leu Pro Lys Lys Glu
1145 1150 1155

Phe Trp Asp Tyr Cys Gln Glu Lys Tyr Gly Lys Ile Glu Lys Glu
1160 1165 1170

Lys Thr Tyr Ala Glu Tyr Phe Ala Glu Val Phe Lys Lys Glu Lys
1175 1180 1185

Glu Ala Leu Ile Lys
1190

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<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> BzoCas13b direct repeat

<400> 76
gttggaactg ctctcatttt ggagggtaat cacaac 36

<210> 77
<211> 3381
<212> DNA
<213> Artificial Sequence

<220>
<223> PbuCas13b nucleic acid sequence

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gacaagcact tctgggccgc ctttctgaac ctggcccgcc acaacgtgta taccacaatc 180
aaccacatca atcggagact ggagatcgcc gagctgaagg acgatggcta tatgatgggc 240
atcaagggca gctggaacga gcaggccaag aagctggaca agaaggtgcg gctgagagat 300
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tcccaaaca ataaggagca gagggagaag gagcagtctg aggccctgag cctgaacaat 420
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cactacaagt attctgagga gagcccaaag cccatcttcg agacatccct gctgaagaac 540
atgtataagg tgtttgacgc caatgtgagg ctggtgaagc gcgattatat gcaccacgag 600
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ctgtccgtgg acctggagct gatcaagtac cagaccacaa gaatcagcat cttcgagatg	3060
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gtgaatagcc tgatcgccgt gcgcaacgcc ttctcccaca atcagtaccc tatgtatgat	3240
gccacactgt ttgccgaggt gaagaagttc accctgtttc caagcgtgga cacaagaag	3300
atcgagctga acatcgcccc ccagctgctg gagatcgtgg gcaaggccat caaggagatc	3360
gagaagtccg agaacaagaa t	3381

<210> 78
 <211> 1127
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PbuCas13b amino acid sequence

 <400> 78

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Phe	Ala	Phe	Pro	Lys	Tyr	Ile	Thr	Ile	Met	Glu	Asn	Lys	Glu	Lys	Pro
			20					25					30		
Glu	Pro	Ile	Tyr	Tyr	Glu	Leu	Thr	Asp	Lys	His	Phe	Trp	Ala	Ala	Phe
		35					40					45			

Leu Asn Leu Ala Arg His Asn Val Tyr Thr Thr Ile Asn His Ile Asn
50 55 60

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

Ile Lys Gly Ser Trp Asn Glu Gln Ala Lys Lys Leu Asp Lys Lys Val
85 90 95

Arg Leu Arg Asp Leu Ile Met Lys His Phe Pro Phe Leu Glu Ala Ala
100 105 110

Ala Tyr Glu Met Thr Asn Ser Lys Ser Pro Asn Asn Lys Glu Gln Arg
115 120 125

Glu Lys Glu Gln Ser Glu Ala Leu Ser Leu Asn Asn Leu Lys Asn Val
130 135 140

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

His Tyr Lys Tyr Ser Glu Glu Ser Pro Lys Pro Ile Phe Glu Thr Ser
165 170 175

Leu Leu Lys Asn Met Tyr Lys Val Phe Asp Ala Asn Val Arg Leu Val
180 185 190

Lys Arg Asp Tyr Met His His Glu Asn Ile Asp Met Gln Arg Asp Phe
195 200 205

Thr His Leu Asn Arg Lys Lys Gln Val Gly Arg Thr Lys Asn Ile Ile
210 215 220

Asp Ser Pro Asn Phe His Tyr His Phe Ala Asp Lys Glu Gly Asn Met
225 230 235 240

Thr Ile Ala Gly Leu Leu Phe Phe Val Ser Leu Phe Leu Asp Lys Lys
245 250 255

Asp Ala Ile Trp Met Gln Lys Lys Leu Lys Gly Phe Lys Asp Gly Arg
260 265 270

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

Ser Leu Pro Lys Leu Lys Leu Glu Asn Val Gln Thr Lys Asp Trp Met
290 295 300

Gln Leu Asp Met Leu Asn Glu Leu Val Arg Cys Pro Lys Ser Leu Tyr
305 310 315 320

Glu Arg Leu Arg Glu Lys Asp Arg Glu Ser Phe Lys Val Pro Phe Asp
325 330 335

Ile Phe Ser Asp Asp Tyr Asn Ala Glu Glu Glu Pro Phe Lys Asn Thr
340 345 350

Leu Val Arg His Gln Asp Arg Phe Pro Tyr Phe Val Leu Arg Tyr Phe
355 360 365

Asp Leu Asn Glu Ile Phe Glu Gln Leu Arg Phe Gln Ile Asp Leu Gly
370 375 380

Thr Tyr His Phe Ser Ile Tyr Asn Lys Arg Ile Gly Asp Glu Asp Glu
385 390 395 400

Val Arg His Leu Thr His His Leu Tyr Gly Phe Ala Arg Ile Gln Asp
405 410 415

Phe Ala Pro Gln Asn Gln Ser Glu Glu Trp Arg Lys Leu Val Lys Asp
420 425 430

Leu Asp His Phe Glu Thr Ser Gln Glu Pro Tyr Ile Ser Lys Thr Ala
435 440 445

Pro His Tyr His Leu Glu Asn Glu Lys Ile Gly Ile Lys Phe Cys Ser
450 455 460

Ala His Asn Asn Leu Phe Pro Ser Leu Gln Thr Asp Lys Thr Cys Asn
465 470 475 480

Gly Arg Ser Lys Phe Asn Leu Gly Thr Gln Phe Thr Ala Glu Ala Phe
485 490 495

Leu Ser Val His Glu Leu Leu Pro Met Met Phe Tyr Tyr Leu Leu Leu
500 505 510

Thr Lys Asp Tyr Ser Arg Lys Glu Ser Ala Asp Lys Val Glu Gly Ile
515 520 525

Ile Arg Lys Glu Ile Ser Asn Ile Tyr Ala Ile Tyr Asp Ala Phe Ala
530 535 540

Asn Asn Glu Ile Asn Ser Ile Ala Asp Leu Thr Arg Arg Leu Gln Asn
545 550 555 560

Thr Asn Ile Leu Gln Gly His Leu Pro Lys Gln Met Ile Ser Ile Leu
565 570 575

Lys Gly Arg Gln Lys Asp Met Gly Lys Glu Ala Glu Arg Lys Ile Gly
580 585 590

Glu Met Ile Asp Asp Thr Gln Arg Arg Leu Asp Leu Leu Cys Lys Gln
595 600 605

Thr Asn Gln Lys Ile Arg Ile Gly Lys Arg Asn Ala Gly Leu Leu Lys
610 615 620

Ser Gly Lys Ile Ala Asp Trp Leu Val Asn Asp Met Met Arg Phe Gln
625 630 635 640

Pro Val Gln Lys Asp Gln Asn Asn Ile Pro Ile Asn Asn Ser Lys Ala
645 650 655

Asn Ser Thr Glu Tyr Arg Met Leu Gln Arg Ala Leu Ala Leu Phe Gly
660 665 670

Ser Glu Asn Phe Arg Leu Lys Ala Tyr Phe Asn Gln Met Asn Leu Val
675 680 685

Gly Asn Asp Asn Pro His Pro Phe Leu Ala Glu Thr Gln Trp Glu His
690 695 700

Gln Thr Asn Ile Leu Ser Phe Tyr Arg Asn Tyr Leu Glu Ala Arg Lys
705 710 715 720

Lys Tyr Leu Lys Gly Leu Lys Pro Gln Asn Trp Lys Gln Tyr Gln His
725 730 735

Phe Leu Ile Leu Lys Val Gln Lys Thr Asn Arg Asn Thr Leu Val Thr
740 745 750

Gly Trp Lys Asn Ser Phe Asn Leu Pro Arg Gly Ile Phe Thr Gln Pro
755 760 765

Ile Arg Glu Trp Phe Glu Lys His Asn Asn Ser Lys Arg Ile Tyr Asp
770 775 780

Gln Ile Leu Ser Phe Asp Arg Val Gly Phe Val Ala Lys Ala Ile Pro
785 790 795 800

Leu Tyr Phe Ala Glu Glu Tyr Lys Asp Asn Val Gln Pro Phe Tyr Asp
805 810 815

Tyr Pro Phe Asn Ile Gly Asn Arg Leu Lys Pro Lys Lys Arg Gln Phe
820 825 830

Leu Asp Lys Lys Glu Arg Val Glu Leu Trp Gln Lys Asn Lys Glu Leu
835 840 845

Phe Lys Asn Tyr Pro Ser Glu Lys Lys Lys Thr Asp Leu Ala Tyr Leu
850 855 860

Asp Phe Leu Ser Trp Lys Lys Phe Glu Arg Glu Leu Arg Leu Ile Lys
865 870 875 880

Asn Gln Asp Ile Val Thr Trp Leu Met Phe Lys Glu Leu Phe Asn Met
885 890 895

Ala Thr Val Glu Gly Leu Lys Ile Gly Glu Ile His Leu Arg Asp Ile
900 905 910

Asp Thr Asn Thr Ala Asn Glu Glu Ser Asn Asn Ile Leu Asn Arg Ile
915 920 925

Met Pro Met Lys Leu Pro Val Lys Thr Tyr Glu Thr Asp Asn Lys Gly
930 935 940

Asn Ile Leu Lys Glu Arg Pro Leu Ala Thr Phe Tyr Ile Glu Glu Thr
945 950 955 960

Glu Thr Lys Val Leu Lys Gln Gly Asn Phe Lys Ala Leu Val Lys Asp
965 970 975

Arg Arg Leu Asn Gly Leu Phe Ser Phe Ala Glu Thr Thr Asp Leu Asn
980 985 990

Leu Glu Glu His Pro Ile Ser Lys Leu Ser Val Asp Leu Glu Leu Ile
995 1000 1005

Lys Tyr Gln Thr Thr Arg Ile Ser Ile Phe Glu Met Thr Leu Gly
1010 1015 1020

Leu Glu Lys Lys Leu Ile Asp Lys Tyr Ser Thr Leu Pro Thr Asp
1025 1030 1035

Ser Phe Arg Asn Met Leu Glu Arg Trp Leu Gln Cys Lys Ala Asn
1040 1045 1050

Arg Pro Glu Leu Lys Asn Tyr Val Asn Ser Leu Ile Ala Val Arg
1055 1060 1065

Asn Ala Phe Ser His Asn Gln Tyr Pro Met Tyr Asp Ala Thr Leu
1070 1075 1080

Phe Ala Glu Val Lys Lys Phe Thr Leu Phe Pro Ser Val Asp Thr
1085 1090 1095

Lys Lys Ile Glu Leu Asn Ile Ala Pro Gln Leu Leu Glu Ile Val
1100 1105 1110

Gly Lys Ala Ile Lys Glu Ile Glu Lys Ser Glu Asn Lys Asn
1115 1120 1125

<210> 79
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> PbuCas13b direct repeat

<400> 79
gttgcacatctg ccttctttttt gaaaggtaaa aacaac 36

<210> 80
<211> 2859
<212> DNA
<213> Artificial Sequence

<220>
<223> AspCas13b nucleic acid sequence

<400> 80
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atgatgttcg gagaggtgga gtctaacca gacaagatcg agaagagcct ggataccctg 180
ccccctgcca tcctgagaca gatcgcctcc tttatctggc tgtctaagga ggaccacccc 240
gataaggcct actccaccga ggaggtgaaa gtgacgtga cagacctggg gcggagactg 300
tgcttttaca ggaattatct cagccactgt ttctatctgg atacacagta cttttattcc 360
gacgagctgg tggataccac agccatcggc gagaagctgc cttacaattt ccaccacttt 420
atcaccaaca gactgttcag gtatagcctg ccagagatca cactgtttcg ctggaacgag 480
ggcgagcggg agtacgagat cctgcgggac ggctgatct tcttttgctg tctgttcctg 540
aagaggggac aggagagcgc gtttctgaat gagctgagat tctttaagag gaccgacgag 600
gagggccgca tcaagcggac catcttcaca aagtattgca caagagagtc tcacaagcac 660
atcggcatcg aggagcagga tttcctgac tttcaggaca tcatcggcga tctgaatagg 720
gtgcctaagg tgtgcgacgg cgtggtggat ctgagcaagg agaacgagag atacatcaag 780
aacagggaga caagcaatga gtctgatgag aacaaggccc ggtatagact gctgatcagg 840
gagaaggaca agtttcccta ctatctgatg cgctacatcg tggatttcgg cgtgctgcct 900

tgcatcacct ttaagcagaa cgactacagc acaaaggagg gccggggcca gttccactat	960
caggatgcag cagtggcaca ggaggagagg tgttacaatt ttgtggtgcg caacggcaac	1020
gtgtactatt cctatatgcc tcaggcccag aacgtggtgc ggatcagcga gctgcagggc	1080
accatctccg tggaggagct gagaaatatg gtgtacgcct ctatcaatgg caaggacgtg	1140
aacaagagcg tggagcagta cctgtatcac ctgcacctgc tgtatgagaa gatcctgacc	1200
atctccggcc agacaatcaa ggagggccgg gtggacgtgg aggattacag acctctgctg	1260
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agcgccgtgg agaagaggct gaaggccatc ctgctgcgcc acgagcagct gctgctgagc	1440
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ttttctgacg atgagaagtt ccggcagcag cctaccgaga agggccacag aggcctgaag	1560
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ggcctgaagc tgtacgataa gctgaaggag tatacccctg agcagctgga gagggaggtg	1860
aagctggtgg tcatgcacgg atacgtgcc gccgccaccc caaagccaaa ggcacaggca	1920
gcaatcccat ctaagctgac agagctgcgg ttctattcct ttctgggcaa gagagagatg	1980
tccttcgccg cctttatccg gcaggacaag aaggcccaga agctgtggct gagaaatttc	2040
tataccgtgg agaacatcaa gacactgcag aagaggcagg ctgccgccga cgcagcctgc	2100
aagaagctgt ataacctggt gggagaggtg gagcgggtgc acaccaacga taagggtgctg	2160
gtgctggtgg cccagaggta tcgcgagcgg ctgctgaatg tgggcagcaa gtgtgccgtg	2220
acactggaca accccgagag gcagcagaag ctggccgacg tgtacgaggt gcagaacgcc	2280
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gacaataggg tgaagcagaa gctgtgcgag gagtgtcgca acgtgcggag aaaggaggat	2460
ctgtgcacct gctgttcccc tcgctactct aatctgacaa gctggctgaa ggagaaccac	2520

tccgagagct ccacgagag ggaggccgcc accatgatgc tgctggacgt ggagcgcaag	2580
ctgctgagct tcctgctgga tgagaggcgc aaggccatca tcgagtacgg caagttcatc	2640
ccattttccg ccctggtgaa ggagtgccgg ctggccgacg caggcctgtg cggcatcaga	2700
aatgacgtgc tgcacgataa cgtgatcagc tacgccgatg ccacggcaa gctgagcgcc	2760
tattttccca aggaggcctc cgaggccgtg gagtacatcc ggagaacaaa ggaggtgcgg	2820
gagcagaggc gcgaggagct gatggccaac tctagccag	2859

<210> 81
 <211> 953
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> AspCas13b amino acid sequence

<400> 81

Met	Ser	Asn	Glu	Ile	Gly	Ala	Phe	Arg	Glu	His	Gln	Phe	Ala	Tyr	Ala
1				5				10						15	

Pro	Gly	Asn	Glu	Lys	Gln	Glu	Glu	Ala	Thr	Phe	Ala	Thr	Tyr	Phe	Asn
		20						25					30		

Leu	Ala	Leu	Ser	Asn	Val	Glu	Gly	Met	Met	Phe	Gly	Glu	Val	Glu	Ser
		35					40					45			

Asn	Pro	Asp	Lys	Ile	Glu	Lys	Ser	Leu	Asp	Thr	Leu	Pro	Pro	Ala	Ile
	50					55					60				

Leu	Arg	Gln	Ile	Ala	Ser	Phe	Ile	Trp	Leu	Ser	Lys	Glu	Asp	His	Pro
65					70				75					80	

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

Val	Arg	Arg	Leu	Cys	Phe	Tyr	Arg	Asn	Tyr	Phe	Ser	His	Cys	Phe	Tyr
			100					105					110		

Leu	Asp	Thr	Gln	Tyr	Phe	Tyr	Ser	Asp	Glu	Leu	Val	Asp	Thr	Thr	Ala
		115					120					125			

Ile Gly Glu Lys Leu Pro Tyr Asn Phe His His Phe Ile Thr Asn Arg
130 135 140

Leu Phe Arg Tyr Ser Leu Pro Glu Ile Thr Leu Phe Arg Trp Asn Glu
145 150 155 160

Gly Glu Arg Lys Tyr Glu Ile Leu Arg Asp Gly Leu Ile Phe Phe Cys
165 170 175

Cys Leu Phe Leu Lys Arg Gly Gln Ala Glu Arg Phe Leu Asn Glu Leu
180 185 190

Arg Phe Phe Lys Arg Thr Asp Glu Glu Gly Arg Ile Lys Arg Thr Ile
195 200 205

Phe Thr Lys Tyr Cys Thr Arg Glu Ser His Lys His Ile Gly Ile Glu
210 215 220

Glu Gln Asp Phe Leu Ile Phe Gln Asp Ile Ile Gly Asp Leu Asn Arg
225 230 235 240

Val Pro Lys Val Cys Asp Gly Val Val Asp Leu Ser Lys Glu Asn Glu
245 250 255

Arg Tyr Ile Lys Asn Arg Glu Thr Ser Asn Glu Ser Asp Glu Asn Lys
260 265 270

Ala Arg Tyr Arg Leu Leu Ile Arg Glu Lys Asp Lys Phe Pro Tyr Tyr
275 280 285

Leu Met Arg Tyr Ile Val Asp Phe Gly Val Leu Pro Cys Ile Thr Phe
290 295 300

Lys Gln Asn Asp Tyr Ser Thr Lys Glu Gly Arg Gly Gln Phe His Tyr
305 310 315 320

Gln Asp Ala Ala Val Ala Gln Glu Glu Arg Cys Tyr Asn Phe Val Val
325 330 335

Arg Asn Gly Asn Val Tyr Tyr Ser Tyr Met Pro Gln Ala Gln Asn Val
340 345 350

Val Arg Ile Ser Glu Leu Gln Gly Thr Ile Ser Val Glu Glu Leu Arg
355 360 365

Asn Met Val Tyr Ala Ser Ile Asn Gly Lys Asp Val Asn Lys Ser Val
370 375 380

Glu Gln Tyr Leu Tyr His Leu His Leu Leu Tyr Glu Lys Ile Leu Thr
385 390 395 400

Ile Ser Gly Gln Thr Ile Lys Glu Gly Arg Val Asp Val Glu Asp Tyr
405 410 415

Arg Pro Leu Leu Asp Lys Leu Leu Leu Arg Pro Ala Ser Asn Gly Glu
420 425 430

Glu Leu Arg Arg Glu Leu Arg Lys Leu Leu Pro Lys Arg Val Cys Asp
435 440 445

Leu Leu Ser Asn Arg Phe Asp Cys Ser Glu Gly Val Ser Ala Val Glu
450 455 460

Lys Arg Leu Lys Ala Ile Leu Leu Arg His Glu Gln Leu Leu Leu Ser
465 470 475 480

Gln Asn Pro Ala Leu His Ile Asp Lys Ile Lys Ser Val Ile Asp Tyr
485 490 495

Leu Tyr Leu Phe Phe Ser Asp Asp Glu Lys Phe Arg Gln Gln Pro Thr
500 505 510

Glu Lys Ala His Arg Gly Leu Lys Asp Glu Glu Phe Gln Met Tyr His
515 520 525

Tyr Leu Val Gly Asp Tyr Asp Ser His Pro Leu Ala Leu Trp Lys Glu
530 535 540

Leu Glu Ala Ser Gly Arg Leu Lys Pro Glu Met Arg Lys Leu Thr Ser
545 550 555 560

Ala Thr Ser Leu His Gly Leu Tyr Met Leu Cys Leu Lys Gly Thr Val
565 570 575

Glu Trp Cys Arg Lys Gln Leu Met Ser Ile Gly Lys Gly Thr Ala Lys
580 585 590

Val Glu Ala Ile Ala Asp Arg Val Gly Leu Lys Leu Tyr Asp Lys Leu
595 600 605

Lys Glu Tyr Thr Pro Glu Gln Leu Glu Arg Glu Val Lys Leu Val Val
610 615 620

Met His Gly Tyr Ala Ala Ala Ala Thr Pro Lys Pro Lys Ala Gln Ala
625 630 635 640

Ala Ile Pro Ser Lys Leu Thr Glu Leu Arg Phe Tyr Ser Phe Leu Gly
645 650 655

Lys Arg Glu Met Ser Phe Ala Ala Phe Ile Arg Gln Asp Lys Lys Ala
660 665 670

Gln Lys Leu Trp Leu Arg Asn Phe Tyr Thr Val Glu Asn Ile Lys Thr
675 680 685

Leu Gln Lys Arg Gln Ala Ala Ala Asp Ala Ala Cys Lys Lys Leu Tyr
690 695 700

Asn Leu Val Gly Glu Val Glu Arg Val His Thr Asn Asp Lys Val Leu
705 710 715 720

Val Leu Val Ala Gln Arg Tyr Arg Glu Arg Leu Leu Asn Val Gly Ser
725 730 735

Lys Cys Ala Val Thr Leu Asp Asn Pro Glu Arg Gln Gln Lys Leu Ala
740 745 750

Asp Val Tyr Glu Val Gln Asn Ala Trp Leu Ser Ile Arg Phe Asp Asp
755 760 765

Leu Asp Phe Thr Leu Thr His Val Asn Leu Ser Asn Leu Arg Lys Ala
770 775 780

Tyr Asn Leu Ile Pro Arg Lys His Ile Leu Ala Phe Lys Glu Tyr Leu
785 790 795 800

Asp Asn Arg Val Lys Gln Lys Leu Cys Glu Glu Cys Arg Asn Val Arg
805 810 815

Arg Lys Glu Asp Leu Cys Thr Cys Cys Ser Pro Arg Tyr Ser Asn Leu
820 825 830

Thr Ser Trp Leu Lys Glu Asn His Ser Glu Ser Ser Ile Glu Arg Glu
835 840 845

Ala Ala Thr Met Met Leu Leu Asp Val Glu Arg Lys Leu Leu Ser Phe
850 855 860

Leu Leu Asp Glu Arg Arg Lys Ala Ile Ile Glu Tyr Gly Lys Phe Ile
865 870 875 880

Pro Phe Ser Ala Leu Val Lys Glu Cys Arg Leu Ala Asp Ala Gly Leu
885 890 895

Cys Gly Ile Arg Asn Asp Val Leu His Asp Asn Val Ile Ser Tyr Ala
900 905 910

Asp Ala Ile Gly Lys Leu Ser Ala Tyr Phe Pro Lys Glu Ala Ser Glu
915 920 925

Ala Val Glu Tyr Ile Arg Arg Thr Lys Glu Val Arg Glu Gln Arg Arg
930 935 940

Glu Glu Leu Met Ala Asn Ser Ser Gln
945 950

<210> 82

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> AspCas13b direct repeat

<400> 82

gctgttatat ccttaccttt gtaagggaag tacagc

36

<210> 83

<211> 3966

<212> DNA

<213> Artificial Sequence

<220>

<223> PsmCas13b nucleic acid sequence

<400> 83

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ttctccatct ctctgaccgg caagcacgtg ttcggcgcct actttaatat ggccagaaca 120

aactttgtga aaaccatcaa ctacatcctg cctatcgccg gcgtgagggg caactatagc 180

gagaatcaga tcaacaagat gctgcacgca ctgttcctga tccaggcagg acgcaatgag 240

gagctgacca cagagcagaa gcagtgggag aagaagctgc ggctgaaccc agagcagcag 300

accaagtttc agaagctgct gttcaagcac tttccagtgc tgggaccaat gatggcagac 360

gtggcagatc acaaggccta tctgaacaag aagaagagca ccgtgcagac agaggacgag 420

acattcgcca tgctgaaggg cgtgtccctg gccgactgcc tggatatcat ctgtctgatg 480

gccgataccc tgacagagtg tagaaacttc tacacacaca aggaccctta taacaagcca 540

agccagctgg ccgatcagta cctgcaccag gagatgatcg ccaagaagct ggacaagggtg 600

gtggtggcct ccaggcgcct cctgaaggat agggagggcc tgtctgtgaa tgaggtggag 660

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aaggtgaagg atggcaaagt gatgaaaacc ttcgtggagt acgacgactt ctacttcaag 780

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ctgatgagcg agctggccgc ctacgaccag tataggtcta ccatcttcat gctgatccag	3660
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aatcagctga ataacgtgga gctgaccgac gatgagcgca agctgctggt ggccatccgg	3840
aacgccttca gccacaattc ctacaacatc gatTTTTTccc tgatcaagga cgtgaagcac	3900
ctgcccaggg tggccaaggg catcctgcag cacctgcagt ctatgctggg cgtggagatc	3960
accaag	3966

<210> 84
 <211> 1322
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PsmCas13b amino acid sequence

 <400> 84

Met	Ser	Lys	Glu	Cys	Lys	Lys	Gln	Arg	Gln	Glu	Lys	Lys	Arg	Arg	Leu
1				5				10					15		

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

Ala Tyr Phe Asn Met Ala Arg Thr Asn Phe Val Lys Thr Ile Asn Tyr
35 40 45

Ile Leu Pro Ile Ala Gly Val Arg Gly Asn Tyr Ser Glu Asn Gln Ile
50 55 60

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

Glu Leu Thr Thr Glu Gln Lys Gln Trp Glu Lys Lys Leu Arg Leu Asn
85 90 95

Pro Glu Gln Gln Thr Lys Phe Gln Lys Leu Leu Phe Lys His Phe Pro
100 105 110

Val Leu Gly Pro Met Met Ala Asp Val Ala Asp His Lys Ala Tyr Leu
115 120 125

Asn Lys Lys Lys Ser Thr Val Gln Thr Glu Asp Glu Thr Phe Ala Met
130 135 140

Leu Lys Gly Val Ser Leu Ala Asp Cys Leu Asp Ile Ile Cys Leu Met
145 150 155 160

Ala Asp Thr Leu Thr Glu Cys Arg Asn Phe Tyr Thr His Lys Asp Pro
165 170 175

Tyr Asn Lys Pro Ser Gln Leu Ala Asp Gln Tyr Leu His Gln Glu Met
180 185 190

Ile Ala Lys Lys Leu Asp Lys Val Val Val Ala Ser Arg Arg Ile Leu
195 200 205

Lys Asp Arg Glu Gly Leu Ser Val Asn Glu Val Glu Phe Leu Thr Gly
210 215 220

Ile Asp His Leu His Gln Glu Val Leu Lys Asp Glu Phe Gly Asn Ala
225 230 235 240

Lys Val Lys Asp Gly Lys Val Met Lys Thr Phe Val Glu Tyr Asp Asp
245 250 255

Phe Tyr Phe Lys Ile Ser Gly Lys Arg Leu Val Asn Gly Tyr Thr Val
260 265 270

Thr Thr Lys Asp Asp Lys Pro Val Asn Val Asn Thr Met Leu Pro Ala
275 280 285

Leu Ser Asp Phe Gly Leu Leu Tyr Phe Cys Val Leu Phe Leu Ser Lys
290 295 300

Pro Tyr Ala Lys Leu Phe Ile Asp Glu Val Arg Leu Phe Glu Tyr Ser
305 310 315 320

Pro Phe Asp Asp Lys Glu Asn Met Ile Met Ser Glu Met Leu Ser Ile
325 330 335

Tyr Arg Ile Arg Thr Pro Arg Leu His Lys Ile Asp Ser His Asp Ser
340 345 350

Lys Ala Thr Leu Ala Met Asp Ile Phe Gly Glu Leu Arg Arg Cys Pro
355 360 365

Met Glu Leu Tyr Asn Leu Leu Asp Lys Asn Ala Gly Gln Pro Phe Phe
370 375 380

His Asp Glu Val Lys His Pro Asn Ser His Thr Pro Asp Val Ser Lys
385 390 395 400

Arg Leu Arg Tyr Asp Asp Arg Phe Pro Thr Leu Ala Leu Arg Tyr Ile
405 410 415

Asp Glu Thr Glu Leu Phe Lys Arg Ile Arg Phe Gln Leu Gln Leu Gly
420 425 430

Ser Phe Arg Tyr Lys Phe Tyr Asp Lys Glu Asn Cys Ile Asp Gly Arg
435 440 445

Val Arg Val Arg Arg Ile Gln Lys Glu Ile Asn Gly Tyr Gly Arg Met
450 455 460

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

Lys Arg Glu Glu Arg Ser Val Lys Leu Glu His Glu Glu Leu Tyr Ile
485 490 495

Asn Leu Asp Gln Phe Leu Glu Asp Thr Ala Asp Ser Thr Pro Tyr Val
500 505 510

Thr Asp Arg Arg Pro Ala Tyr Asn Ile His Ala Asn Arg Ile Gly Leu
515 520 525

Tyr Trp Glu Asp Ser Gln Asn Pro Lys Gln Tyr Lys Val Phe Asp Glu
530 535 540

Asn Gly Met Tyr Ile Pro Glu Leu Val Val Thr Glu Asp Lys Lys Ala
545 550 555 560

Pro Ile Lys Met Pro Ala Pro Arg Cys Ala Leu Ser Val Tyr Asp Leu
565 570 575

Pro Ala Met Leu Phe Tyr Glu Tyr Leu Arg Glu Gln Gln Asp Asn Glu
580 585 590

Phe Pro Ser Ala Glu Gln Val Ile Ile Glu Tyr Glu Asp Asp Tyr Arg
595 600 605

Lys Phe Phe Lys Ala Val Ala Glu Gly Lys Leu Lys Pro Phe Lys Arg
610 615 620

Pro Lys Glu Phe Arg Asp Phe Leu Lys Lys Glu Tyr Pro Lys Leu Arg
625 630 635 640

Met Ala Asp Ile Pro Lys Lys Leu Gln Leu Phe Leu Cys Ser His Gly
645 650 655

Leu Cys Tyr Asn Asn Lys Pro Glu Thr Val Tyr Glu Arg Leu Asp Arg
660 665 670

Leu Thr Leu Gln His Leu Glu Glu Arg Glu Leu His Ile Gln Asn Arg
675 680 685

Leu Glu His Tyr Gln Lys Asp Arg Asp Met Ile Gly Asn Lys Asp Asn
690 695 700

Gln Tyr Gly Lys Lys Ser Phe Ser Asp Val Arg His Gly Ala Leu Ala
705 710 715 720

Arg Tyr Leu Ala Gln Ser Met Met Glu Trp Gln Pro Thr Lys Leu Lys
725 730 735

Asp Lys Glu Lys Gly His Asp Lys Leu Thr Gly Leu Asn Tyr Asn Val
740 745 750

Leu Thr Ala Tyr Leu Ala Thr Tyr Gly His Pro Gln Val Pro Glu Glu
755 760 765

Gly Phe Thr Pro Arg Thr Leu Glu Gln Val Leu Ile Asn Ala His Leu
770 775 780

Ile Gly Gly Ser Asn Pro His Pro Phe Ile Asn Lys Val Leu Ala Leu
785 790 795 800

Gly Asn Arg Asn Ile Glu Glu Leu Tyr Leu His Tyr Leu Glu Glu Glu
805 810 815

Leu Lys His Ile Arg Ser Arg Ile Gln Ser Leu Ser Ser Asn Pro Ser
820 825 830

Asp Lys Ala Leu Ser Ala Leu Pro Phe Ile His His Asp Arg Met Arg
835 840 845

Tyr His Glu Arg Thr Ser Glu Glu Met Met Ala Leu Ala Ala Arg Tyr
850 855 860

Thr Thr Ile Gln Leu Pro Asp Gly Leu Phe Thr Pro Tyr Ile Leu Glu
865 870 875 880

Ile Leu Gln Lys His Tyr Thr Glu Asn Ser Asp Leu Gln Asn Ala Leu
885 890 895

Ser Gln Asp Val Pro Val Lys Leu Asn Pro Thr Cys Asn Ala Ala Tyr
900 905 910

Leu Ile Thr Leu Phe Tyr Gln Thr Val Leu Lys Asp Asn Ala Gln Pro
915 920 925

Phe Tyr Leu Ser Asp Lys Thr Tyr Thr Arg Asn Lys Asp Gly Glu Lys
930 935 940

Ala Glu Ser Phe Ser Phe Lys Arg Ala Tyr Glu Leu Phe Ser Val Leu
945 950 955 960

Asn Asn Asn Lys Lys Asp Thr Phe Pro Phe Glu Met Ile Pro Leu Phe
965 970 975

Leu Thr Ser Asp Glu Ile Gln Glu Arg Leu Ser Ala Lys Leu Leu Asp
980 985 990

Gly Asp Gly Asn Pro Val Pro Glu Val Gly Glu Lys Gly Lys Pro Ala
995 1000 1005

Thr Asp Ser Gln Gly Asn Thr Ile Trp Lys Arg Arg Ile Tyr Ser
1010 1015 1020

Glu Val Asp Asp Tyr Ala Glu Lys Leu Thr Asp Arg Asp Met Lys
1025 1030 1035

Ile Ser Phe Lys Gly Glu Trp Glu Lys Leu Pro Arg Trp Lys Gln
1040 1045 1050

Asp Lys Ile Ile Lys Arg Arg Asp Glu Thr Arg Arg Gln Met Arg
1055 1060 1065

Asp Glu Leu Leu Gln Arg Met Pro Arg Tyr Ile Arg Asp Ile Lys
1070 1075 1080

Asp Asn Glu Arg Thr Leu Arg Arg Tyr Lys Thr Gln Asp Met Val
1085 1090 1095

Leu Phe Leu Leu Ala Glu Lys Met Phe Thr Asn Ile Ile Ser Glu
1100 1105 1110

Gln Ser Ser Glu Phe Asn Trp Lys Gln Met Arg Leu Ser Lys Val
1115 1120 1125

Cys Asn Glu Ala Phe Leu Arg Gln Thr Leu Thr Phe Arg Val Pro
1130 1135 1140

Val Thr Val Gly Glu Thr Thr Ile Tyr Val Glu Gln Glu Asn Met
1145 1150 1155

Ser Leu Lys Asn Tyr Gly Glu Phe Tyr Arg Phe Leu Thr Asp Asp
1160 1165 1170

Arg Leu Met Ser Leu Leu Asn Asn Ile Val Glu Thr Leu Lys Pro
1175 1180 1185

Asn Glu Asn Gly Asp Leu Val Ile Arg His Thr Asp Leu Met Ser
1190 1195 1200

Glu Leu Ala Ala Tyr Asp Gln Tyr Arg Ser Thr Ile Phe Met Leu
1205 1210 1215

Ile Gln Ser Ile Glu Asn Leu Ile Ile Thr Asn Asn Ala Val Leu
1220 1225 1230

Asp Asp Pro Asp Ala Asp Gly Phe Trp Val Arg Glu Asp Leu Pro
1235 1240 1245

Lys Arg Asn Asn Phe Ala Ser Leu Leu Glu Leu Ile Asn Gln Leu
1250 1255 1260

Asn Asn Val Glu Leu Thr Asp Asp Glu Arg Lys Leu Leu Val Ala
1265 1270 1275

Ile Arg Asn Ala Phe Ser His Asn Ser Tyr Asn Ile Asp Phe Ser
1280 1285 1290

Leu Ile Lys Asp Val Lys His Leu Pro Glu Val Ala Lys Gly Ile
1295 1300 1305

Leu Gln His Leu Gln Ser Met Leu Gly Val Glu Ile Thr Lys
1310 1315 1320

<210> 85
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> PsmCas13b direct repeat

<400> 85
gttgtagaag cttatcgttt ggataggtat gacaac 36

<210> 86
<211> 3285
<212> DNA
<213> Artificial Sequence

<220>
<223> RanCas13b nucleic acid sequence

<400> 86
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ggcctgaaaa cccccagcaa cgacgataag atcgtggacg tgggtgtgcga gacatggaac 180
aatatcctga acaatgacca cgatctgctg aagaagtccc agctgaccga gctgatcctg 240
aagcacttcc cttttctgac agccatgtgc taccaccccc ctaagaagga gggcaagaag 300
aagggccacc agaaggagca gcagaaggag aaggagagcg aggcacagtc ccaggcagag 360
gccctgaacc catccaagct gatcgaggcc ctggagatcc tggatgaatca gctgcactct 420
ctgcggaact actatagcca ctataagcac aagaagcccc acgccgagaa ggatatcttc 480
aagcacctgt ataaggcctt cgacgcctct ctgagaatgg tgaaggagga ttataaggcc 540
cacttcaccg tgaatctgac aagggacttt gccacactga accgcaaggg caagaacaag 600
caggacaatc ccgacttcaa cagatacaga ttcgagaagg atggcttctt taccgagtct 660
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aaggtgtccg gcttcaaggc ctctcacaag cagcgcgaga agatgaccac agaggtgttt	780
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atgctgctgg atatgctgtc tgagctgagc agatgtccta agctgctgta tgagaagctg	900
agcgaggaga ataagaagca cttccaggtg gaggccgacg gcttttctgga tgagatcgag	960
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gccctgaggt atctggacct gaatgagtcc ttcaagtcta tccgctttca ggtggatctg	1080
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ttcaccgtgg cccagcccac cacagaggag aaggatggcc tgggaatcgc agaggccctg	3240
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<210> 87

<211> 1095

<212> PRT

<213> Artificial Sequence

<220>

<223> RanCas13b amino acid sequence

<400> 87

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1				5					10					15	

Phe	Trp	Gly	Ala	Phe	Leu	Asn	Ile	Ala	Arg	His	Asn	Ala	Phe	Ile	Thr
			20					25					30		

Ile	Cys	His	Ile	Asn	Glu	Gln	Leu	Gly	Leu	Lys	Thr	Pro	Ser	Asn	Asp
			35				40					45			

Asp Lys Ile Val Asp Val Val Cys Glu Thr Trp Asn Asn Ile Leu Asn
50 55 60

Asn Asp His Asp Leu Leu Lys Lys Ser Gln Leu Thr Glu Leu Ile Leu
65 70 75 80

Lys His Phe Pro Phe Leu Thr Ala Met Cys Tyr His Pro Pro Lys Lys
85 90 95

Glu Gly Lys Lys Lys Gly His Gln Lys Glu Gln Gln Lys Glu Lys Glu
100 105 110

Ser Glu Ala Gln Ser Gln Ala Glu Ala Leu Asn Pro Ser Lys Leu Ile
115 120 125

Glu Ala Leu Glu Ile Leu Val Asn Gln Leu His Ser Leu Arg Asn Tyr
130 135 140

Tyr Ser His Tyr Lys His Lys Lys Pro Asp Ala Glu Lys Asp Ile Phe
145 150 155 160

Lys His Leu Tyr Lys Ala Phe Asp Ala Ser Leu Arg Met Val Lys Glu
165 170 175

Asp Tyr Lys Ala His Phe Thr Val Asn Leu Thr Arg Asp Phe Ala His
180 185 190

Leu Asn Arg Lys Gly Lys Asn Lys Gln Asp Asn Pro Asp Phe Asn Arg
195 200 205

Tyr Arg Phe Glu Lys Asp Gly Phe Phe Thr Glu Ser Gly Leu Leu Phe
210 215 220

Phe Thr Asn Leu Phe Leu Asp Lys Arg Asp Ala Tyr Trp Met Leu Lys
225 230 235 240

Lys Val Ser Gly Phe Lys Ala Ser His Lys Gln Arg Glu Lys Met Thr
245 250 255

Thr Glu Val Phe Cys Arg Ser Arg Ile Leu Leu Pro Lys Leu Arg Leu
260 265 270

Glu Ser Arg Tyr Asp His Asn Gln Met Leu Leu Asp Met Leu Ser Glu
275 280 285

Leu Ser Arg Cys Pro Lys Leu Leu Tyr Glu Lys Leu Ser Glu Glu Asn
290 295 300

Lys Lys His Phe Gln Val Glu Ala Asp Gly Phe Leu Asp Glu Ile Glu
305 310 315 320

Glu Glu Gln Asn Pro Phe Lys Asp Thr Leu Ile Arg His Gln Asp Arg
325 330 335

Phe Pro Tyr Phe Ala Leu Arg Tyr Leu Asp Leu Asn Glu Ser Phe Lys
340 345 350

Ser Ile Arg Phe Gln Val Asp Leu Gly Thr Tyr His Tyr Cys Ile Tyr
355 360 365

Asp Lys Lys Ile Gly Asp Glu Gln Glu Lys Arg His Leu Thr Arg Thr
370 375 380

Leu Leu Ser Phe Gly Arg Leu Gln Asp Phe Thr Glu Ile Asn Arg Pro
385 390 395 400

Gln Glu Trp Lys Ala Leu Thr Lys Asp Leu Asp Tyr Lys Glu Thr Ser
405 410 415

Asn Gln Pro Phe Ile Ser Lys Thr Thr Pro His Tyr His Ile Thr Asp
420 425 430

Asn Lys Ile Gly Phe Arg Leu Gly Thr Ser Lys Glu Leu Tyr Pro Ser
435 440 445

Leu Glu Ile Lys Asp Gly Ala Asn Arg Ile Ala Lys Tyr Pro Tyr Asn
450 455 460

Ser Gly Phe Val Ala His Ala Phe Ile Ser Val His Glu Leu Leu Pro
465 470 475 480

Leu Met Phe Tyr Gln His Leu Thr Gly Lys Ser Glu Asp Leu Leu Lys
485 490 495

Glu Thr Val Arg His Ile Gln Arg Ile Tyr Lys Asp Phe Glu Glu Glu
500 505 510

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

Pro Leu Gly Ala Phe Pro Lys Gln Met Leu Gly Leu Leu Gln Asn Lys
530 535 540

Gln Pro Asp Leu Ser Glu Lys Ala Lys Ile Lys Ile Glu Lys Leu Ile
545 550 555 560

Ala Glu Thr Lys Leu Leu Ser His Arg Leu Asn Thr Lys Leu Lys Ser
565 570 575

Ser Pro Lys Leu Gly Lys Arg Arg Glu Lys Leu Ile Lys Thr Gly Val
580 585 590

Leu Ala Asp Trp Leu Val Lys Asp Phe Met Arg Phe Gln Pro Val Ala
595 600 605

Tyr Asp Ala Gln Asn Gln Pro Ile Lys Ser Ser Lys Ala Asn Ser Thr
610 615 620

Glu Phe Trp Phe Ile Arg Arg Ala Leu Ala Leu Tyr Gly Gly Glu Lys
625 630 635 640

Asn Arg Leu Glu Gly Tyr Phe Lys Gln Thr Asn Leu Ile Gly Asn Thr
645 650 655

Asn Pro His Pro Phe Leu Asn Lys Phe Asn Trp Lys Ala Cys Arg Asn
660 665 670

Leu Val Asp Phe Tyr Gln Gln Tyr Leu Glu Gln Arg Glu Lys Phe Leu
675 680 685

Glu Ala Ile Lys Asn Gln Pro Trp Glu Pro Tyr Gln Tyr Cys Leu Leu
690 695 700

Leu Lys Ile Pro Lys Glu Asn Arg Lys Asn Leu Val Lys Gly Trp Glu
705 710 715 720

Gln Gly Gly Ile Ser Leu Pro Arg Gly Leu Phe Thr Glu Ala Ile Arg
725 730 735

Glu Thr Leu Ser Glu Asp Leu Met Leu Ser Lys Pro Ile Arg Lys Glu
740 745 750

Ile Lys Lys His Gly Arg Val Gly Phe Ile Ser Arg Ala Ile Thr Leu
755 760 765

Tyr Phe Lys Glu Lys Tyr Gln Asp Lys His Gln Ser Phe Tyr Asn Leu
770 775 780

Ser Tyr Lys Leu Glu Ala Lys Ala Pro Leu Leu Lys Arg Glu Glu His
785 790 795 800

Tyr Glu Tyr Trp Gln Gln Asn Lys Pro Gln Ser Pro Thr Glu Ser Gln
805 810 815

Arg Leu Glu Leu His Thr Ser Asp Arg Trp Lys Asp Tyr Leu Leu Tyr
820 825 830

Lys Arg Trp Gln His Leu Glu Lys Lys Leu Arg Leu Tyr Arg Asn Gln
835 840 845

Asp Val Met Leu Trp Leu Met Thr Leu Glu Leu Thr Lys Asn His Phe
850 855 860

Lys Glu Leu Asn Leu Asn Tyr His Gln Leu Lys Leu Glu Asn Leu Ala
865 870 875 880

Val Asn Val Gln Glu Ala Asp Ala Lys Leu Asn Pro Leu Asn Gln Thr
885 890 895

Leu Pro Met Val Leu Pro Val Lys Val Tyr Pro Ala Thr Ala Phe Gly
900 905 910

Glu Val Gln Tyr His Lys Thr Pro Ile Arg Thr Val Tyr Ile Arg Glu
915 920 925

Glu His Thr Lys Ala Leu Lys Met Gly Asn Phe Lys Ala Leu Val Lys
930 935 940

Asp Arg Arg Leu Asn Gly Leu Phe Ser Phe Ile Lys Glu Glu Asn Asp
945 950 955 960

Thr Gln Lys His Pro Ile Ser Gln Leu Arg Leu Arg Arg Glu Leu Glu
965 970 975

Ile Tyr Gln Ser Leu Arg Val Asp Ala Phe Lys Glu Thr Leu Ser Leu
980 985 990

Glu Glu Lys Leu Leu Asn Lys His Thr Ser Leu Ser Ser Leu Glu Asn
995 1000 1005

Glu Phe Arg Ala Leu Leu Glu Glu Trp Lys Lys Glu Tyr Ala Ala
1010 1015 1020

Ser Ser Met Val Thr Asp Glu His Ile Ala Phe Ile Ala Ser Val
1025 1030 1035

Arg Asn Ala Phe Cys His Asn Gln Tyr Pro Phe Tyr Lys Glu Ala
1040 1045 1050

Leu His Ala Pro Ile Pro Leu Phe Thr Val Ala Gln Pro Thr Thr
1055 1060 1065

Glu Glu Lys Asp Gly Leu Gly Ile Ala Glu Ala Leu Leu Lys Val
1070 1075 1080

Leu Arg Glu Tyr Cys Glu Ile Val Lys Ser Gln Ile
1085 1090 1095

<210> 88
<211> 36
<212> DNA
<213> Artificial Sequence

<220>

<223> RanCas13b direct repeat

<400> 88

gttgggactg ctctcacttt gaagggtatt cacaac

36

<210> 89

<211> 3372

<212> DNA

<213> Artificial Sequence

<220>

<223> PauCas13b nucleic acid sequence

<400> 89

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tgggccgcct ttctgaacct ggcccggcac aacgtgtata tcaccatcaa ccacatcaat 120

aagctgctgg agatccggga gatcgacaac gatgagaagg tgctggacat caagaccctg 180

tggcagaagg gcaacaagga tctgaatcag aaggccaggc tgcgcgagct gatgacaaag 240

cacttcccct tcctggagac agccatctac acaaagaaca aggaggataa gaaggaggtg 300

aagcaggaga agcaggccga ggcccagtct ctggagagcc tgaaggactg cctgttcctg 360

tttctggata agctgcagga ggcccgaat tactatagcc actacaagta ttccgagttc 420

tctaaggagc cagagtttga ggagggcctg ctggagaaga tgtataacat ctttggcaac 480

aatatccagc tggatcatcaa cgactatcag cacaacaagg atatcaatcc cgacgaggat 540

ttcaagcacc tggaccggaa gggccagttc aagtactcct ttgccgataa cgagggcaat 600

atcaccgagt ccggcctgct gttcttcgtg agcctgttcc tggagaagaa ggacgccatc 660

tggatgcagc agaagctgaa cggctttaag gataacctgg agaacaagaa gaagatgaca 720

cacgaggtgt tctgccggag cagaatcctg atgcccaagc tgcgcctgga gagcaccag 780

acacaggact ggattctgct ggacatgctg aatgagctga tccggtgtcc taagtccctg 840

tacgagagac tgcagggcga cgataggag aagttcaagg tgccatttga ccccgccgac 900

gaggattaca acgccgagca ggagcctttt aagaataccc tgatcagaca ccaggacagg 960

ttcccatact ttgtgctgag atacttcgat tacaacgaga tcttcaagaa tctgaggttt 1020

cagatcgacc tgggcaccta ccacttctct atctataaga agctgatcgg cggccagaag 1080

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aagcccttca gcctgtatac cgccaacaat tccgaggaga agggcctggg catcgccaac	3300
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gagacaaagg ag	3372

<210> 90
 <211> 1124
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PauCas13 amino acid sequence

 <400> 90

Met	Glu	Asp	Asp	Lys	Lys	Thr	Thr	Gly	Ser	Ile	Ser	Tyr	Glu	Leu	Lys
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			20					25					30		
Tyr	Ile	Thr	Ile	Asn	His	Ile	Asn	Lys	Leu	Leu	Glu	Ile	Arg	Glu	Ile
		35					40					45			
Asp	Asn	Asp	Glu	Lys	Val	Leu	Asp	Ile	Lys	Thr	Leu	Trp	Gln	Lys	Gly
	50					55					60				
Asn	Lys	Asp	Leu	Asn	Gln	Lys	Ala	Arg	Leu	Arg	Glu	Leu	Met	Thr	Lys
65					70				75					80	

His Phe Pro Phe Leu Glu Thr Ala Ile Tyr Thr Lys Asn Lys Glu Asp
85 90 95

Lys Lys Glu Val Lys Gln Glu Lys Gln Ala Glu Ala Gln Ser Leu Glu
100 105 110

Ser Leu Lys Asp Cys Leu Phe Leu Phe Leu Asp Lys Leu Gln Glu Ala
115 120 125

Arg Asn Tyr Tyr Ser His Tyr Lys Tyr Ser Glu Phe Ser Lys Glu Pro
130 135 140

Glu Phe Glu Glu Gly Leu Leu Glu Lys Met Tyr Asn Ile Phe Gly Asn
145 150 155 160

Asn Ile Gln Leu Val Ile Asn Asp Tyr Gln His Asn Lys Asp Ile Asn
165 170 175

Pro Asp Glu Asp Phe Lys His Leu Asp Arg Lys Gly Gln Phe Lys Tyr
180 185 190

Ser Phe Ala Asp Asn Glu Gly Asn Ile Thr Glu Ser Gly Leu Leu Phe
195 200 205

Phe Val Ser Leu Phe Leu Glu Lys Lys Asp Ala Ile Trp Met Gln Gln
210 215 220

Lys Leu Asn Gly Phe Lys Asp Asn Leu Glu Asn Lys Lys Lys Met Thr
225 230 235 240

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

Glu Ser Thr Gln Thr Gln Asp Trp Ile Leu Leu Asp Met Leu Asn Glu
260 265 270

Leu Ile Arg Cys Pro Lys Ser Leu Tyr Glu Arg Leu Gln Gly Asp Asp
275 280 285

Arg Glu Lys Phe Lys Val Pro Phe Asp Pro Ala Asp Glu Asp Tyr Asn
290 295 300

Ala Glu Gln Glu Pro Phe Lys Asn Thr Leu Ile Arg His Gln Asp Arg
305 310 315 320

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

Asn Leu Arg Phe Gln Ile Asp Leu Gly Thr Tyr His Phe Ser Ile Tyr
340 345 350

Lys Lys Leu Ile Gly Gly Gln Lys Glu Asp Arg His Leu Thr His Lys
355 360 365

Leu Tyr Gly Phe Glu Arg Ile Gln Glu Phe Ala Lys Gln Asn Arg Pro
370 375 380

Asp Glu Trp Lys Ala Ile Val Lys Asp Leu Asp Thr Tyr Glu Thr Ser
385 390 395 400

Asn Lys Arg Tyr Ile Ser Glu Thr Thr Pro His Tyr His Leu Glu Asn
405 410 415

Gln Lys Ile Gly Ile Arg Phe Arg Asn Gly Asn Lys Glu Ile Trp Pro
420 425 430

Ser Leu Lys Thr Asn Asp Glu Asn Asn Glu Lys Ser Lys Tyr Lys Leu
435 440 445

Asp Lys Gln Tyr Gln Ala Glu Ala Phe Leu Ser Val His Glu Leu Leu
450 455 460

Pro Met Met Phe Tyr Tyr Leu Leu Leu Lys Lys Glu Lys Pro Asn Asn
465 470 475 480

Asp Glu Ile Asn Ala Ser Ile Val Glu Gly Phe Ile Lys Arg Glu Ile
485 490 495

Arg Asn Ile Phe Lys Leu Tyr Asp Ala Phe Ala Asn Gly Glu Ile Asn
500 505 510

Asn Ile Asp Asp Leu Glu Lys Tyr Cys Ala Asp Lys Gly Ile Pro Lys
515 520 525

Arg His Leu Pro Lys Gln Met Val Ala Ile Leu Tyr Asp Glu His Lys
530 535 540

Asp Met Val Lys Glu Ala Lys Arg Lys Gln Lys Glu Met Val Lys Asp
545 550 555 560

Thr Lys Lys Leu Leu Ala Thr Leu Glu Lys Gln Thr Gln Lys Glu Lys
565 570 575

Glu Asp Asp Gly Arg Asn Val Lys Leu Leu Lys Ser Gly Glu Ile Ala
580 585 590

Arg Trp Leu Val Asn Asp Met Met Arg Phe Gln Pro Val Gln Lys Asp
595 600 605

Asn Glu Gly Lys Pro Leu Asn Asn Ser Lys Ala Asn Ser Thr Glu Tyr
610 615 620

Gln Met Leu Gln Arg Ser Leu Ala Leu Tyr Asn Asn Glu Glu Lys Pro
625 630 635 640

Thr Arg Tyr Phe Arg Gln Val Asn Leu Ile Glu Ser Asn Asn Pro His
645 650 655

Pro Phe Leu Lys Trp Thr Lys Trp Glu Glu Cys Asn Asn Ile Leu Thr
660 665 670

Phe Tyr Tyr Ser Tyr Leu Thr Lys Lys Ile Glu Phe Leu Asn Lys Leu
675 680 685

Lys Pro Glu Asp Trp Lys Lys Asn Gln Tyr Phe Leu Lys Leu Met Glu
690 695 700

Pro Lys Thr Asn Arg Glu Thr Leu Val Gln Gly Trp Lys Asn Gly Phe
705 710 715 720

Asn Leu Pro Arg Gly Ile Phe Thr Glu Pro Ile Arg Glu Trp Phe Lys
725 730 735

Arg His Gln Asn Asn Ser Lys Glu Tyr Glu Lys Val Glu Ala Leu Asp
740 745 750

Arg Val Gly Leu Val Thr Lys Val Ile Pro Leu Phe Phe Lys Glu Glu
755 760 765

Tyr Phe Lys Asp Lys Glu Glu Asn Phe Lys Glu Asp Thr Gln Lys Glu
770 775 780

Ile Asn Asp Cys Val Gln Pro Phe Tyr Asn Phe Pro Tyr Asn Val Gly
785 790 795 800

Asn Ile His Lys Pro Lys Glu Lys Asp Phe Leu His Arg Glu Glu Arg
805 810 815

Ile Glu Leu Trp Asp Lys Lys Lys Asp Lys Phe Lys Gly Tyr Lys Glu
820 825 830

Lys Ile Lys Ser Lys Lys Leu Thr Glu Lys Asp Lys Glu Glu Phe Arg
835 840 845

Ser Tyr Leu Glu Phe Gln Ser Trp Asn Lys Phe Glu Arg Glu Leu Arg
850 855 860

Leu Val Arg Asn Gln Asp Ile Val Thr Trp Leu Leu Cys Lys Glu Leu
865 870 875 880

Ile Asp Lys Leu Lys Ile Asp Glu Leu Asn Ile Glu Glu Leu Lys Lys
885 890 895

Leu Arg Leu Asn Asn Ile Asp Thr Asp Thr Ala Lys Lys Glu Lys Asn
900 905 910

Asn Ile Leu Asn Arg Val Met Pro Met Glu Leu Pro Val Thr Val Tyr
915 920 925

Glu Ile Asp Asp Ser His Lys Ile Val Lys Asp Lys Pro Leu His Thr
930 935 940

Ile Tyr Ile Lys Glu Ala Glu Thr Lys Leu Leu Lys Gln Gly Asn Phe
945 950 955 960

Lys Ala Leu Val Lys Asp Arg Arg Leu Asn Gly Leu Phe Ser Phe Val
965 970 975

Lys Thr Asn Ser Glu Ala Glu Ser Lys Arg Asn Pro Ile Ser Lys Leu
980 985 990

Arg Val Glu Tyr Glu Leu Gly Glu Tyr Gln Glu Ala Arg Ile Glu Ile
995 1000 1005

Ile Gln Asp Met Leu Ala Leu Glu Glu Lys Leu Ile Asn Lys Tyr
1010 1015 1020

Lys Asp Leu Pro Thr Asn Lys Phe Ser Glu Met Leu Asn Ser Trp
1025 1030 1035

Leu Glu Gly Lys Asp Glu Ala Asp Lys Ala Arg Phe Gln Asn Asp
1040 1045 1050

Val Asp Phe Leu Ile Ala Val Arg Asn Ala Phe Ser His Asn Gln
1055 1060 1065

Tyr Pro Met His Asn Lys Ile Glu Phe Ala Asn Ile Lys Pro Phe
1070 1075 1080

Ser Leu Tyr Thr Ala Asn Asn Ser Glu Glu Lys Gly Leu Gly Ile
1085 1090 1095

Ala Asn Gln Leu Lys Asp Lys Thr Lys Glu Thr Thr Asp Lys Ile
1100 1105 1110

Lys Lys Ile Glu Lys Pro Ile Glu Thr Lys Glu
1115 1120

<210> 91

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> PauCas13b direct repeat

<400> 91

gttgatatctg ccttctgttt gaaaggtaaa aacaac

36

<210> 92

<211> 1422

<212> DNA

<213> Artificial Sequence

<220>

<223> CMV-BD-2xms2-PPT-exon-MMP9_intron2-2xms2-BD-bGHpA

<400> 92

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gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc attgacgtca 180

atgggtggag tattttacggt aaactgccc cttggcagta catcaagtgt atcatatgcc 240

aagtacgcc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta 300

catgacctta tgggactttc ctacttggca gtacatctac gtattagtca tcgctattac 360

catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg actcacgggg 420

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 480

ggactttcca aaatgtcgt acaactccgc ccattgacg caaatgggcg gtaggcgtgt 540

acgggtgggag gtctatataa gcagagctgg tttagtgaac cgtcggatct tccatttcgg 600

gtgtcgtgac gtacgaatac gatctagacc ctgcatcctc tctgggacac tcaacaccct 660

cacggacagc ccgaattcga cccaagctga cgggagcaca tgaggatcac ccatgtgcca 720

cgagcgacat gaggatcacc catgtcgctt tcactagtct gtggtgtgat atccatggcg 780

gcctacttat cctgtccctt ttttttccac aggagcgcac catcttcttc aaggacgacg 840

gcaactacaa gaccgcgcc gaggtgaagt tcgagggcga caccctgggtg aaccgcatcg 900

agctgaaggg catcgacttc aaggaggacg gcaacatcct ggggcacaag ctggagtaca 960

actacaacag ccacaacgtc tatatcatgg ccgacaagca gaagaacggc atcaaggtga 1020

gccggggctg tgaaagctgc gggatggagc gagaaggcct gatctggctc ttgagcctgc 1080

aacggagcac atgaggatca cccatgtgcc acgagcgaca tgaggatcac ccatgtcgaa 1140

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<210> 93
 <211> 5403
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PspCas13b-ABI1-2a-PYL1-MS2 nucleic acid sequence

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gccaagaacg gctacgaaa gcagcccgag aaaaccatgt tcatcatcga gcggctgcag	240
agctacttcc cattcctgaa gatcatggcc gagaaccaga gagagtacag caacggcaag	300
tacaagcaga accgcgtgga agtgaacagc aacgacatct tcgaggtgct gaagcgcgcc	360
ttcggcgtgc tgaagatgta cagggacctg accaacgcat acaagacctg cgaggaaaag	420
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tccaagtga ataccggatt cttcctgagc ctgcaggact acaacggcga cacacagaag	660
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gaaaggatct ggaccgttgt tttggaatct tatgttggtg atgtaccgga aggtaattcg	4860
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gagctcacta tcccaatttt cgctaccaat tctgactgtg aactcatcgt gaaggcaatg	5340
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tac	5403

<210> 94
 <211> 1801
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> PspCas13b-ABI1-2a-PYL1-MS2 amino acid sequeunce

 <400> 94

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20 25 30

Gln Lys Val Ala Asp Ile Glu Gly Glu Gln Asn Glu Asn Asn Glu Asn
35 40 45

Leu Trp Phe His Pro Val Met Ser His Leu Tyr Asn Ala Lys Asn Gly
50 55 60

Tyr Asp Lys Gln Pro Glu Lys Thr Met Phe Ile Ile Glu Arg Leu Gln
65 70 75 80

Ser Tyr Phe Pro Phe Leu Lys Ile Met Ala Glu Asn Gln Arg Glu Tyr
85 90 95

Ser Asn Gly Lys Tyr Lys Gln Asn Arg Val Glu Val Asn Ser Asn Asp
100 105 110

Ile Phe Glu Val Leu Lys Arg Ala Phe Gly Val Leu Lys Met Tyr Arg
115 120 125

Asp Leu Thr Asn Ala Tyr Lys Thr Tyr Glu Glu Lys Leu Asn Asp Gly
130 135 140

Cys Glu Phe Leu Thr Ser Thr Glu Gln Pro Leu Ser Gly Met Ile Asn
145 150 155 160

Asn Tyr Tyr Thr Val Ala Leu Arg Asn Met Asn Glu Arg Tyr Gly Tyr
165 170 175

Lys Thr Glu Asp Leu Ala Phe Ile Gln Asp Lys Arg Phe Lys Phe Val
180 185 190

Lys Asp Ala Tyr Gly Lys Lys Lys Ser Gln Val Asn Thr Gly Phe Phe
195 200 205

Leu Ser Leu Gln Asp Tyr Asn Gly Asp Thr Gln Lys Lys Leu His Leu
210 215 220

Ser Gly Val Gly Ile Ala Leu Leu Ile Cys Leu Phe Leu Asp Lys Gln
225 230 235 240

Tyr Ile Asn Ile Phe Leu Ser Arg Leu Pro Ile Phe Ser Ser Tyr Asn
245 250 255

Ala Gln Ser Glu Glu Arg Arg Ile Ile Ile Arg Ser Phe Gly Ile Asn
260 265 270

Ser Ile Lys Leu Pro Lys Asp Arg Ile His Ser Glu Lys Ser Asn Lys
275 280 285

Ser Val Ala Met Asp Met Leu Asn Glu Val Lys Arg Cys Pro Asp Glu
290 295 300

Leu Phe Thr Thr Leu Ser Ala Glu Lys Gln Ser Arg Phe Arg Ile Ile
305 310 315 320

Ser Asp Asp His Asn Glu Val Leu Met Lys Arg Ser Ser Asp Arg Phe
325 330 335

Val Pro Leu Leu Leu Gln Tyr Ile Asp Tyr Gly Lys Leu Phe Asp His
340 345 350

Ile Arg Phe His Val Asn Met Gly Lys Leu Arg Tyr Leu Leu Lys Ala
355 360 365

Asp Lys Thr Cys Ile Asp Gly Gln Thr Arg Val Arg Val Ile Glu Gln
370 375 380

Pro Leu Asn Gly Phe Gly Arg Leu Glu Glu Ala Glu Thr Met Arg Lys
385 390 395 400

Gln Glu Asn Gly Thr Phe Gly Asn Ser Gly Ile Arg Ile Arg Asp Phe
405 410 415

Glu Asn Met Lys Arg Asp Asp Ala Asn Pro Ala Asn Tyr Pro Tyr Ile
420 425 430

Val Asp Thr Tyr Thr His Tyr Ile Leu Glu Asn Asn Lys Val Glu Met
435 440 445

Phe Ile Asn Asp Lys Glu Asp Ser Ala Pro Leu Leu Pro Val Ile Glu
450 455 460

Asp Asp Arg Tyr Val Val Lys Thr Ile Pro Ser Cys Arg Met Ser Thr
465 470 475 480

Leu Glu Ile Pro Ala Met Ala Phe His Met Phe Leu Phe Gly Ser Lys
485 490 495

Lys Thr Glu Lys Leu Ile Val Asp Val His Asn Arg Tyr Lys Arg Leu
500 505 510

Phe Gln Ala Met Gln Lys Glu Glu Val Thr Ala Glu Asn Ile Ala Ser
515 520 525

Phe Gly Ile Ala Glu Ser Asp Leu Pro Gln Lys Ile Leu Asp Leu Ile
530 535 540

Ser Gly Asn Ala His Gly Lys Asp Val Asp Ala Phe Ile Arg Leu Thr
545 550 555 560

Val Asp Asp Met Leu Thr Asp Thr Glu Arg Arg Ile Lys Arg Phe Lys
565 570 575

Asp Asp Arg Lys Ser Ile Arg Ser Ala Asp Asn Lys Met Gly Lys Arg
580 585 590

Gly Phe Lys Gln Ile Ser Thr Gly Lys Leu Ala Asp Phe Leu Ala Lys
595 600 605

Asp Ile Val Leu Phe Gln Pro Ser Val Asn Asp Gly Glu Asn Lys Ile
610 615 620

Thr Gly Leu Asn Tyr Arg Ile Met Gln Ser Ala Ile Ala Val Tyr Asp
625 630 635 640

Ser Gly Asp Asp Tyr Glu Ala Lys Gln Gln Phe Lys Leu Met Phe Glu
645 650 655

Lys Ala Arg Leu Ile Gly Lys Gly Thr Thr Glu Pro His Pro Phe Leu
660 665 670

Tyr Lys Val Phe Ala Arg Ser Ile Pro Ala Asn Ala Val Glu Phe Tyr
675 680 685

Glu Arg Tyr Leu Ile Glu Arg Lys Phe Tyr Leu Thr Gly Leu Ser Asn
690 695 700

Glu Ile Lys Lys Gly Asn Arg Val Asp Val Pro Phe Ile Arg Arg Asp
705 710 715 720

Gln Asn Lys Trp Lys Thr Pro Ala Met Lys Thr Leu Gly Arg Ile Tyr
725 730 735

Ser Glu Asp Leu Pro Val Glu Leu Pro Arg Gln Met Phe Asp Asn Glu
740 745 750

Ile Lys Ser His Leu Lys Ser Leu Pro Gln Met Glu Gly Ile Asp Phe
755 760 765

Asn Asn Ala Asn Val Thr Tyr Leu Ile Ala Glu Tyr Met Lys Arg Val
770 775 780

Leu Asp Asp Asp Phe Gln Thr Phe Tyr Gln Trp Asn Arg Asn Tyr Arg
785 790 795 800

Tyr Met Asp Met Leu Lys Gly Glu Tyr Asp Arg Lys Gly Ser Leu Gln
805 810 815

His Cys Phe Thr Ser Val Glu Glu Arg Glu Gly Leu Trp Lys Glu Arg
820 825 830

Ala Ser Arg Thr Glu Arg Tyr Arg Lys Gln Ala Ser Asn Lys Ile Arg
835 840 845

Ser Asn Arg Gln Met Arg Asn Ala Ser Ser Glu Glu Ile Glu Thr Ile
850 855 860

Leu Asp Lys Arg Leu Ser Asn Ser Arg Asn Glu Tyr Gln Lys Ser Glu
865 870 875 880

Lys Val Ile Arg Arg Tyr Arg Val Gln Asp Ala Leu Leu Phe Leu Leu
885 890 895

Ala Lys Lys Thr Leu Thr Glu Leu Ala Asp Phe Asp Gly Glu Arg Phe
900 905 910

Lys Leu Lys Glu Ile Met Pro Asp Ala Glu Lys Gly Ile Leu Ser Glu
915 920 925

Ile Met Pro Met Ser Phe Thr Phe Glu Lys Gly Gly Lys Lys Tyr Thr
930 935 940

Ile Thr Ser Glu Gly Met Lys Leu Lys Asn Tyr Gly Asp Phe Phe Val
945 950 955 960

Leu Ala Ser Asp Lys Arg Ile Gly Asn Leu Leu Glu Leu Val Gly Ser
965 970 975

Asp Ile Val Ser Lys Glu Asp Ile Met Glu Glu Phe Asn Lys Tyr Asp
980 985 990

Gln Cys Arg Pro Glu Ile Ser Ser Ile Val Phe Asn Leu Glu Lys Trp
995 1000 1005

Ala Phe Asp Thr Tyr Pro Glu Leu Ser Ala Arg Val Asp Arg Glu
1010 1015 1020

Glu Lys Val Asp Phe Lys Ser Ile Leu Lys Ile Leu Leu Asn Asn
1025 1030 1035

Lys Asn Ile Asn Lys Glu Gln Ser Asp Ile Leu Arg Lys Ile Arg
1040 1045 1050

Asn Ala Phe Asp Ala Asn Asn Tyr Pro Asp Lys Gly Val Val Glu
1055 1060 1065

Ile Lys Ala Leu Pro Glu Ile Ala Met Ser Ile Lys Lys Ala Phe
1070 1075 1080

Gly Glu Tyr Ala Ile Met Lys Gly Ser Leu Gln Ala Tyr Pro Tyr
1085 1090 1095

Asp Val Pro Asp Tyr Ala Ser Leu Gly Ser Gly Ser Pro Lys Lys
1100 1105 1110

Lys Arg Lys Val Glu Asp Pro Lys Lys Lys Arg Lys Val Asp Gly
1115 1120 1125

Ile Gly Ser Gly Ser Asn Gly Gly Gly Gly Ser Gly Pro Arg Thr
1130 1135 1140

Arg Val Pro Leu Tyr Gly Phe Thr Ser Ile Cys Gly Arg Arg Pro
1145 1150 1155

Glu Met Glu Ala Ala Val Ser Thr Ile Pro Arg Phe Leu Gln Ser
1160 1165 1170

Ser Ser Gly Ser Met Leu Asp Gly Arg Phe Asp Pro Gln Ser Ala
1175 1180 1185

Ala His Phe Phe Gly Val Tyr Asp Gly His Gly Gly Ser Gln Val
1190 1195 1200

Ala Asn Tyr Cys Arg Glu Arg Met His Leu Ala Leu Ala Glu Glu
1205 1210 1215

Ile Ala Lys Glu Lys Pro Met Leu Cys Asp Gly Asp Thr Trp Leu
1220 1225 1230

Glu Lys Trp Lys Lys Ala Leu Phe Asn Ser Phe Leu Arg Val Asp
1235 1240 1245

Ser Glu Ile Glu Ser Val Ala Pro Glu Thr Val Gly Ser Thr Ser
1250 1255 1260

Val Val Ala Val Val Phe Pro Ser His Ile Phe Val Ala Asn Cys
1265 1270 1275

Gly Asp Ser Arg Ala Val Leu Cys Arg Gly Lys Thr Ala Leu Pro
1280 1285 1290

Leu Ser Val Asp His Lys Pro Asp Arg Glu Asp Glu Ala Ala Arg
1295 1300 1305

Ile Glu Ala Ala Gly Gly Lys Val Ile Gln Trp Asn Gly Ala Arg
1310 1315 1320

Val Phe Gly Val Leu Ala Met Ser Arg Ser Ile Gly Asp Arg Tyr
1325 1330 1335

Leu Lys Pro Ser Ile Ile Pro Asp Pro Glu Val Thr Ala Val Lys
1340 1345 1350

Arg Val Lys Glu Asp Asp Cys Leu Ile Leu Ala Ser Asp Gly Val
1355 1360 1365

Trp Asp Val Met Thr Asp Glu Glu Ala Cys Glu Met Ala Arg Lys
1370 1375 1380

Arg Ile Leu Leu Trp His Lys Lys Asn Ala Val Ala Gly Asp Ala
1385 1390 1395

Ser Leu Leu Ala Asp Glu Arg Arg Lys Glu Gly Lys Asp Pro Ala
1400 1405 1410

Ala Met Ser Ala Ala Glu Tyr Leu Ser Lys Leu Ala Ile Gln Arg
1415 1420 1425

Gly Ser Lys Asp Asn Ile Ser Val Val Val Val Asp Leu Lys Gly
1430 1435 1440

Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1445 1450 1455

Glu Glu Asn Pro Gly Pro Met Gly Gly Gly Ala Pro Thr Gln Asp
1460 1465 1470

Glu Phe Thr Gln Leu Ser Gln Ser Ile Ala Glu Phe His Thr Tyr
1475 1480 1485

Gln Leu Gly Asn Gly Arg Cys Ser Ser Leu Leu Ala Gln Arg Ile
1490 1495 1500

His Ala Pro Pro Glu Thr Val Trp Ser Val Val Arg Arg Phe Asp
1505 1510 1515

Arg Pro Gln Ile Tyr Lys His Phe Ile Lys Ser Cys Asn Val Ser
1520 1525 1530

Glu Asp Phe Glu Met Arg Val Gly Cys Thr Arg Asp Val Asn Val
1535 1540 1545

Ile Ser Gly Leu Pro Ala Asn Thr Ser Arg Glu Arg Leu Asp Leu
1550 1555 1560

Leu Asp Asp Asp Arg Arg Val Thr Gly Phe Ser Ile Thr Gly Gly
1565 1570 1575

Glu His Arg Leu Arg Asn Tyr Lys Ser Val Thr Thr Val His Arg
1580 1585 1590

Phe Glu Lys Glu Glu Glu Glu Glu Arg Ile Trp Thr Val Val Leu
1595 1600 1605

Glu Ser Tyr Val Val Asp Val Pro Glu Gly Asn Ser Glu Glu Asp
1610 1615 1620

Thr Arg Leu Phe Ala Asp Thr Val Ile Arg Leu Asn Leu Gln Lys
1625 1630 1635

Leu Ala Ser Ile Thr Glu Ala Met Asn Glu Phe Ser Ser Ala Ala
1640 1645 1650

Gly Thr Ser Pro Lys Lys Lys Arg Lys Val Gly Gly Ser Gly Gly
1655 1660 1665

Gly Gly Ser Met Ala Ser Asn Phe Thr Gln Phe Val Leu Val Asp
1670 1675 1680

Asn Gly Gly Thr Gly Asp Val Thr Val Ala Pro Ser Asn Phe Ala
1685 1690 1695

Asn Gly Val Ala Glu Trp Ile Ser Ser Asn Ser Arg Ser Gln Ala
1700 1705 1710

Tyr Lys Val Thr Cys Ser Val Arg Gln Ser Ser Ala Gln Lys Arg
1715 1720 1725

Lys Tyr Thr Ile Lys Val Glu Val Pro Lys Val Ala Thr Gln Thr
1730 1735 1740

Val Gly Gly Val Glu Leu Pro Val Ala Ala Trp Arg Ser Tyr Leu
1745 1750 1755

Asn Met Glu Leu Thr Ile Pro Ile Phe Ala Thr Asn Ser Asp Cys
1760 1765 1770

Glu Leu Ile Val Lys Ala Met Gln Gly Leu Leu Lys Asp Gly Asn
1775 1780 1785

Pro Ile Pro Ser Ala Ile Ala Ala Asn Ser Gly Ile Tyr
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<210> 95
<211> 3414
<212> DNA
<213> Artificial Sequence

<220>
<223> dRfxCas13d-MS2 nucleic acid sequence

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gccgaaggca gcgacgccag gctggaaaag atcgtggagg gcgacagcat caggagcgtg 180
aatgagggcg aggccttcag cgctgaaatg gccgataaaa acgccggcta taagatcggc 240
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gagagcgtg atggcaatga caatatttgt atccaggtga tccataacat cctggacatt 420
gaaaaaatcc tcgccgaata cattaccaac gccgcctacg ccgtcaacaa tatctccggc 480
ctggataagg acattattgg attcggcaag ttctccacag tgtataccta cgacgaattc 540

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caggcctttt tcagcaagga gggcagaaat tacatcatca attacggcaa cgaatgctat	720
gacattctgg ccctcctgag cggactggcg cactgggtgg tcgctaacaa cgaagaagag	780
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gccgaacaat atttcagatt cagcattatg aaagagcaga aaaacctcgg attcaatatc	1020
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atcccaattt tcgctaccaa ttctgactgt gaatcatcg tgaaggcaat gcaggggctc	3360
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<210> 96

<211> 1138

<212> PRT

<213> Artificial Sequence

<220>

<223> dRfxCas13d-MS2 amino acid sequence

<400> 96

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Lys Ser Phe Ala Lys Gly Met Gly Val Lys Ser Thr Leu Val Ser Gly
20 25 30

Ser Lys Val Tyr Met Thr Thr Phe Ala Glu Gly Ser Asp Ala Arg Leu
35 40 45

Glu Lys Ile Val Glu Gly Asp Ser Ile Arg Ser Val Asn Glu Gly Glu
50 55 60

Ala Phe Ser Ala Glu Met Ala Asp Lys Asn Ala Gly Tyr Lys Ile Gly
65 70 75 80

Asn Ala Lys Phe Ser His Pro Lys Gly Tyr Ala Val Val Ala Asn Asn
85 90 95

Pro Leu Tyr Thr Gly Pro Val Gln Gln Asp Met Leu Gly Leu Lys Glu
100 105 110

Thr Leu Glu Lys Arg Tyr Phe Gly Glu Ser Ala Asp Gly Asn Asp Asn
115 120 125

Ile Cys Ile Gln Val Ile His Asn Ile Leu Asp Ile Glu Lys Ile Leu
130 135 140

Ala Glu Tyr Ile Thr Asn Ala Ala Tyr Ala Val Asn Asn Ile Ser Gly
145 150 155 160

Leu Asp Lys Asp Ile Ile Gly Phe Gly Lys Phe Ser Thr Val Tyr Thr
165 170 175

Tyr Asp Glu Phe Lys Asp Pro Glu His His Arg Ala Ala Phe Asn Asn
180 185 190

Asn Asp Lys Leu Ile Asn Ala Ile Lys Ala Gln Tyr Asp Glu Phe Asp
195 200 205

Asn Phe Leu Asp Asn Pro Arg Leu Gly Tyr Phe Gly Gln Ala Phe Phe
210 215 220

Ser Lys Glu Gly Arg Asn Tyr Ile Ile Asn Tyr Gly Asn Glu Cys Tyr
225 230 235 240

Asp Ile Leu Ala Leu Leu Ser Gly Leu Ala His Trp Val Val Ala Asn
245 250 255

Asn Glu Glu Glu Ser Arg Ile Ser Arg Thr Trp Leu Tyr Asn Leu Asp
260 265 270

Lys Asn Leu Asp Asn Glu Tyr Ile Ser Thr Leu Asn Tyr Leu Tyr Asp
275 280 285

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

Asn Val Asn Tyr Ile Ala Glu Thr Leu Gly Ile Asn Pro Ala Glu Phe
305 310 315 320

Ala Glu Gln Tyr Phe Arg Phe Ser Ile Met Lys Glu Gln Lys Asn Leu
325 330 335

Gly Phe Asn Ile Thr Lys Leu Arg Glu Val Met Leu Asp Arg Lys Asp
340 345 350

Met Ser Glu Ile Arg Lys Asn His Lys Val Phe Asp Ser Ile Arg Thr
355 360 365

Lys Val Tyr Thr Met Met Asp Phe Val Ile Tyr Arg Tyr Tyr Ile Glu
370 375 380

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

Lys Ser Leu Ser Glu Lys Asp Ile Phe Val Ile Asn Leu Arg Gly Ser
405 410 415

Phe Asn Asp Asp Gln Lys Asp Ala Leu Tyr Tyr Asp Glu Ala Asn Arg
420 425 430

Ile Trp Arg Lys Leu Glu Asn Ile Met His Asn Ile Lys Glu Phe Arg
435 440 445

Gly Asn Lys Thr Arg Glu Tyr Lys Lys Lys Asp Ala Pro Arg Leu Pro
450 455 460

Arg Ile Leu Pro Ala Gly Arg Asp Val Ser Ala Phe Ser Lys Leu Met
465 470 475 480

Tyr Ala Leu Thr Met Phe Leu Asp Gly Lys Glu Ile Asn Asp Leu Leu
485 490 495

Thr Thr Leu Ile Asn Lys Phe Asp Asn Ile Gln Ser Phe Leu Lys Val
500 505 510

Met Pro Leu Ile Gly Val Asn Ala Lys Phe Val Glu Glu Tyr Ala Phe
515 520 525

Phe Lys Asp Ser Ala Lys Ile Ala Asp Glu Leu Arg Leu Ile Lys Ser
530 535 540

Phe Ala Arg Met Gly Glu Pro Ile Ala Asp Ala Arg Arg Ala Met Tyr
545 550 555 560

Ile Asp Ala Ile Arg Ile Leu Gly Thr Asn Leu Ser Tyr Asp Glu Leu
565 570 575

Lys Ala Leu Ala Asp Thr Phe Ser Leu Asp Glu Asn Gly Asn Lys Leu
580 585 590

Lys Lys Gly Lys His Gly Met Arg Asn Phe Ile Ile Asn Asn Val Ile
595 600 605

Ser Asn Lys Arg Phe His Tyr Leu Ile Arg Tyr Gly Asp Pro Ala His
610 615 620

Leu His Glu Ile Ala Lys Asn Glu Ala Val Val Lys Phe Val Leu Gly
625 630 635 640

Arg Ile Ala Asp Ile Gln Lys Lys Gln Gly Gln Asn Gly Lys Asn Gln
645 650 655

Ile Asp Arg Tyr Tyr Glu Thr Cys Ile Gly Lys Asp Lys Gly Lys Ser
660 665 670

Val Ser Glu Lys Val Asp Ala Leu Thr Lys Ile Ile Thr Gly Met Asn
675 680 685

Tyr Asp Gln Phe Asp Lys Lys Arg Ser Val Ile Glu Asp Thr Gly Arg
690 695 700

Glu Asn Ala Glu Arg Glu Lys Phe Lys Lys Ile Ile Ser Leu Tyr Leu
705 710 715 720

Thr Val Ile Tyr His Ile Leu Lys Asn Ile Val Asn Ile Asn Ala Arg
725 730 735

Tyr Val Ile Gly Phe His Cys Val Glu Arg Asp Ala Gln Leu Tyr Lys
740 745 750

Glu Lys Gly Tyr Asp Ile Asn Leu Lys Lys Leu Glu Glu Lys Gly Phe
755 760 765

Ser Ser Val Thr Lys Leu Cys Ala Gly Ile Asp Glu Thr Ala Pro Asp
770 775 780

Lys Arg Lys Asp Val Glu Lys Glu Met Ala Glu Arg Ala Lys Glu Ser
785 790 795 800

Ile Asp Ser Leu Glu Ser Ala Asn Pro Lys Leu Tyr Ala Asn Tyr Ile
805 810 815

Lys Tyr Ser Asp Glu Lys Lys Ala Glu Glu Phe Thr Arg Gln Ile Asn
820 825 830

Arg Glu Lys Ala Lys Thr Ala Leu Asn Ala Tyr Leu Arg Asn Thr Lys
835 840 845

Trp Asn Val Ile Ile Arg Glu Asp Leu Leu Arg Ile Asp Asn Lys Thr
850 855 860

Cys Thr Leu Phe Ala Asn Lys Ala Val Ala Leu Glu Val Ala Arg Tyr
865 870 875 880

Val His Ala Tyr Ile Asn Asp Ile Ala Glu Val Asn Ser Tyr Phe Gln
885 890 895

Leu Tyr His Tyr Ile Met Gln Arg Ile Ile Met Asn Glu Arg Tyr Glu
900 905 910

Lys Ser Ser Gly Lys Val Ser Glu Tyr Phe Asp Ala Val Asn Asp Glu
915 920 925

Lys Lys Tyr Asn Asp Arg Leu Leu Lys Leu Leu Cys Val Pro Phe Gly
930 935 940

Tyr Cys Ile Pro Arg Phe Lys Asn Leu Ser Ile Glu Ala Leu Phe Asp
945 950 955 960

Arg Asn Glu Ala Ala Lys Phe Asp Lys Glu Lys Lys Lys Val Ser Gly
965 970 975

Asn Ser Gly Ser Gly Pro Lys Lys Lys Arg Lys Val Ala Ala Ala Tyr
980 985 990

Pro Tyr Asp Val Pro Asp Tyr Ala Ala Gly Ser Gly Gly Gly Gly Ser
995 1000 1005

Met Ala Ser Asn Phe Thr Gln Phe Val Leu Val Asp Asn Gly Gly
1010 1015 1020

Thr Gly Asp Val Thr Val Ala Pro Ser Asn Phe Ala Asn Gly Val
1025 1030 1035

Ala Glu Trp Ile Ser Ser Asn Ser Arg Ser Gln Ala Tyr Lys Val
1040 1045 1050

Thr Cys Ser Val Arg Gln Ser Ser Ala Gln Lys Arg Lys Tyr Thr
1055 1060 1065

Ile Lys Val Glu Val Pro Lys Val Ala Thr Gln Thr Val Gly Gly
1070 1075 1080

Val Glu Leu Pro Val Ala Ala Trp Arg Ser Tyr Leu Asn Met Glu
1085 1090 1095

Leu Thr Ile Pro Ile Phe Ala Thr Asn Ser Asp Cys Glu Leu Ile
1100 1105 1110

Val Lys Ala Met Gln Gly Leu Leu Lys Asp Gly Asn Pro Ile Pro
1115 1120 1125

Ser Ala Ile Ala Ala Asn Ser Gly Ile Tyr
1130 1135

<210> 97
<211> 3411
<212> DNA
<213> Artificial Sequence

<220>
<223> MS2-dRfxCas13d nucleic acid sequence

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 aagaggaagg tggcggccgc ttaccatac gatgttccag attacgctgc t 3411

<210> 98

<211> 1137

<212> PRT

<213> Artificial Sequence

<220>

<223> MS2-dRfxCas13d amino acid sequence

<400> 98

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Gly Asp Val Thr Val Ala Pro Ser Asn Phe Ala Asn Gly Val Ala Glu
 20 25 30

Trp Ile Ser Ser Asn Ser Arg Ser Gln Ala Tyr Lys Val Thr Cys Ser
 35 40 45

Val Arg Gln Ser Ser Ala Gln Lys Arg Lys Tyr Thr Ile Lys Val Glu
50 55 60

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

Ala Ala Trp Arg Ser Tyr Leu Asn Met Glu Leu Thr Ile Pro Ile Phe
85 90 95

Ala Thr Asn Ser Asp Cys Glu Leu Ile Val Lys Ala Met Gln Gly Leu
100 105 110

Leu Lys Asp Gly Asn Pro Ile Pro Ser Ala Ile Ala Ala Asn Ser Gly
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Ile Tyr Gly Ser Gly Gly Gly Gly Ser Ser Pro Lys Lys Lys Arg Lys
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Val Glu Ala Ser Ile Glu Lys Lys Lys Ser Phe Ala Lys Gly Met Gly
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Val Lys Ser Thr Leu Val Ser Gly Ser Lys Val Tyr Met Thr Thr Phe
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Ala Glu Gly Ser Asp Ala Arg Leu Glu Lys Ile Val Glu Gly Asp Ser
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Ile Arg Ser Val Asn Glu Gly Glu Ala Phe Ser Ala Glu Met Ala Asp
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Lys Asn Ala Gly Tyr Lys Ile Gly Asn Ala Lys Phe Ser His Pro Lys
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Gly Tyr Ala Val Val Ala Asn Asn Pro Leu Tyr Thr Gly Pro Val Gln
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Glu Ser Ala Asp Gly Asn Asp Asn Ile Cys Ile Gln Val Ile His Asn
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Ile Leu Asp Ile Glu Lys Ile Leu Ala Glu Tyr Ile Thr Asn Ala Ala
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Tyr Ala Val Asn Asn Ile Ser Gly Leu Asp Lys Asp Ile Ile Gly Phe
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Gly Lys Phe Ser Thr Val Tyr Thr Tyr Asp Glu Phe Lys Asp Pro Glu
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Lys Ala Gln Tyr Asp Glu Phe Asp Asn Phe Leu Asp Asn Pro Arg Leu
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Arg Thr Trp Leu Tyr Asn Leu Asp Lys Asn Leu Asp Asn Glu Tyr Ile
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Ser Thr Leu Asn Tyr Leu Tyr Asp Arg Ile Thr Asn Glu Leu Thr Asn
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Ser Phe Ser Lys Asn Ser Ala Ala Asn Val Asn Tyr Ile Ala Glu Thr
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Leu Gly Ile Asn Pro Ala Glu Phe Ala Glu Gln Tyr Phe Arg Phe Ser
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Leu Tyr Tyr Asp Glu Ala Asn Arg Ile Trp Arg Lys Leu Glu Asn Ile
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Met His Asn Ile Lys Glu Phe Arg Gly Asn Lys Thr Arg Glu Tyr Lys
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725 730 735

Asn Phe Ile Ile Asn Asn Val Ile Ser Asn Lys Arg Phe His Tyr Leu
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755 760 765

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820 825 830

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