195. The method of Claim 96, comprising introducing a nucleic acid of Claim 180 or a vector of Claim 181 into said sample under conditions in which said Cas9 polypeptide is expressed.

196. The method of Claim 194 or 195, further comprising introducing a single guide RNA.

197. The method of any one of Claims 194-196, further comprising introducing an antisense oligonucleotide.

198. The method of any one of Claims 194-197, wherein said sample comprises a tissue.

199. The method of any one of Claims 194-198, wherein said sample comprises a plurality of cells.

200. The method of any one of Claims 194-199, comprising modifying a target RNA in said sample.

201. The method of Claim 200, wherein said target RNA comprises a repeat sequence.

202. The method of Claim 201, wherein said repeat sequence is selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof.

203. The method of Claim 201 or 202, wherein said repeat sequence is associated with a disease.

204. The method of Claim 203, wherein said disease is selected from the group consisting of myotonic dystrophy, Huntington's disease, familial ALS, cancer, spinal muscular atrophy and Fragile X syndrome.

[0006a] In one aspect, the present disclosure refers to an engineered nucleoprotein complex comprising: (a) a nuclease-inactive RNA-targeted Cas9 (RCas9) polypeptide, wherein the nuclease-inactive RCas9 polypeptide: (1) lacks all or part of an HNH domain, all or part of at least one RuvC nuclease domain, all or part of a Cas9 polypeptide DNase active site, all or part of a ββα-metal fold comprising a Cas9 polypeptide active site, or a combination thereof as compared to a corresponding wild type (WT) Cas9 polypeptide; (2) lacks DNase, DNA cleaving capability or activity, or nickase activity; and (3) lacks all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide

Dnase active site, a ββα-metal fold that comprising a Cas9 polypeptide active site, or combinations thereof; further wherein the nuclease-inactive Rcas9 polypeptide has a reduced polypeptide size as compared to a corresponding wild type (WT) Cas9 polypeptide that permits packaging of the RCas9-coding nucleotide in a delivery vector; and (b) a recombinant or synthetic single guide RNA (sgRNA) comprising: (1) on its 5' end, an RNA sequence that hybridizes to or binds to a target RNA sequence having at least 60% complementarity to the sgRNA 5' end, wherein the target RNA sequence comprises a repeat sequence, wherein the RNA sequence that hybridizes to or binds to the target RNA sequence is capable of hybridizing or binding to the repeat sequence, and wherein the repeat sequence is CUG, CCUG, CAG, GGGGCC, or any combination thereof; and (2) on its 3' end: (i) an RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide, or (ii) a linker that covalently links or non-covalently links the 5' RNA sequence of the sgRNA with the nuclease-inactive RCas9 polypeptide,wherein the RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide comprises or is derived from the wild type guide RNA of an archaeal or a bacterial organism from which RCas9 is derived; and wherein optionally the nucleoprotein complex does not comprise a PAMmer oligonucleotide.

[0006b] In another aspect, the present disclosure refers to a first nucleic acid encoding the nuclease-inactive RCas9 polypeptide as disclosed herein and a second nucleic acid encoding the sgRNA as disclosed herein.

[0006c] In another aspect, the present disclosure refers to a chimeric nucleic acid encoding the engineered nucleoprotein complex as disclosed herein.

[0006d] In another aspect, the present disclosure refers to a cell comprising: (a) the engineered nucleoprotein complex as disclosed herein; or a nucleic acid as disclosed herein, or nucleic acid as disclosed herein, wherein the cell is a mammalian cell or a human cell.

[0006e] In another aspect, the present disclosure refers to a pharmaceutical composition comprising: (a) the engineered nucleoprotein complex as disclosed herein or (b) a nucleic acids as disclosed herein, or the nucleic acid as disclosed herein, wherein optionally the pharmaceutical compound is formulated for enteral or parenteral delivery, or for intravenous (IV) delivery.

[0006f] In another aspect, the present disclosure refers to a use of the engineered nucleoprotein complex of the disclosure, the nucleic acids of the disclosure or the nucleic acid of the disclosure, the cell of the disclosure, or the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating, preventing, ameliorating or reducing a symptom of a disease or condition, or an infection, in a mammalian or a human subject.

[0006g] In another aspect, the present disclosure refers to a method of expressing the engineered nucleoprotein complex as disclosed herein, comprising introducing the nucleic acids of the disclosure or the nucleic acid of the disclosure into a cell *in vitro* under conditions in which said cell expresses said nucleoprotein complex.

[0006h] In another aspect, the present disclosure refers to a vector comprising the nucleic acids of the disclosure or the nucleic acid of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1. *S. pyogenes* Cas9 and single guide RNA (sgRNA) complexes bound to DNA or RNA. A: The Cas9:sgRNA complex may require a DNA NGG motif referred to as the protospacer adjacent motif (PAM). In the case of DNA binding, the PAM is supplied by the DNA target itself. The mechanism of DNA targeting by Cas9 is described extensively (Sander JD, Joung JK. CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat Biotechnol.* 2014;32(4):347-55; Sternberg SH, Redding S, Jinek M, Greene

WHAT IS CLAIMED IS:

1. An engineered nucleoprotein complex comprising:

(a) ~~a Cas9 polypeptide,~~ a nuclease-inactive RNA-targeted Cas9 (RCas9) polypeptide, wherein the nuclease-inactive RCas9 polypeptide:

(1) lacks all or part of an HNH domain, all or part of at least one RuvC nuclease domain, all or part of a Cas9 polypeptide DNase active site, all or part of a ββα-metal fold comprising a Cas9 polypeptide active site, or a combination thereof as compared to a corresponding wild type (WT) Cas9 polypeptide;

(2) lacks DNase, DNA cleaving capability or activity, or nickase activity; and

(3) lacks all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide Dnase active site, a ββα-metal fold that comprising a Cas9 polypeptide active site, or combinations thereof; further wherein the nuclease-inactive Rcas9 polypeptide has a reduced polypeptide size as compared to a corresponding wild type (WT) Cas9 polypeptide that permits packaging of the RCas9-coding nucleotide in a delivery vector;

and

(b) a recombinant or synthetic single guide RNA (sgRNA) comprising ~~which is engineered or designed to comprise~~:

(1) on its 5' end, an RNA sequence ~~that recognizes by hybridization (~~that hybridizes to or binds to~~)~~ a target RNA sequence having at least 60% complementarity to the sgRNA 5' end, wherein the target RNA sequence comprises a repeat sequence, wherein the RNA sequence that hybridizes to or binds to the target RNA sequence is capable of hybridizing or binding to the repeat sequence, and wherein the repeat sequence is CUG, CCUG, CAG, GGGGCC, or any combination thereof;

and

(2) on its 3' end:

(i) an RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide ~~Cas9 polypeptide (a Cas9 polypeptide binding "scaffold sequence")~~, or

(ii) a linker that ~~binds or~~ covalently links or non-covalently links the 5' RNA ~~hybridizing or binding end of~~ sequence of the sgRNA with the ~~Cas9~~ nuclease-inactive RCas9 polypeptide,

wherein the RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide comprises or is derived from the wild type guide RNA of an archaeal or a bacterial organism from which RCas9 is derived;

and wherein ~~optionally~~ the nucleoprotein complex does not comprise a PAMmer oligonucleotide.~~,~~

~~and optionally the Cas9 polypeptide:~~

~~(6) is a, or is derived from a, bacterial or archaeal Cas9 polypeptide,~~

~~(7) lacks a domain, or a portion of a domain, of a corresponding wild type (WT) Cas9 polypeptide, wherein optionally the domain is an HNH and/or RuvC nuclease domain of Cas9, comprises a ββα-metal fold comprising or including a Cas9 polypeptide active site, or combinations thereof;~~

~~(8) lacks DNase, or DNA cleaving, capability or activity, nickase activity, or combinations thereof, wherein optionally the DNase, or DNA cleaving capability or activity is removed by modification (mutation) or removal of all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide DNase active site or a ββα-metal fold that comprising a Cas9 polypeptide active site, or combinations thereof,~~

~~(9) lacks all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide DNase active site, a ββα-metal fold that comprising a Cas9 polypeptide active site, or combinations thereof, thereby optionally reducing the size of the polypeptide, optionally facilitating packaging of a Cas9-coding nucleotide in a viral or other delivery vector, or~~

~~(10) is a variant of a WT Cas9 polypeptide, and has one or more amino acid mutations that result in reduced DNase or nuclease activity relative to a corresponding WT Cas9 polypeptide,~~

2. The engineered nucleoprotein complex of claim 1, wherein the nuclease-inactive RCas9 polypeptide or the RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide of the sgRNA comprises a sequence isolated or derived from an ~~or optionally the~~ archaeal or bacterial Cas9 polypeptide isolated~~, comprises~~ or ~~is~~ derived from selected from the groups consisting of~~:~~ ~~a~~ *Haloferax mediteranii*, ~~a~~ *Mycobacterium tuberculosis*, ~~a~~ *Francisella tularensis* subsp. *novicida*, ~~a~~ *Pasteurella multocida*, ~~a~~ *Neisseria meningitidis*, ~~a~~ *Campylobacter jejune*, ~~a~~ *Streptococcus thermophilus* LMD-9 CRISPR 3, ~~a~~ *Campylobacter lari* CF89-12, ~~a~~ *Mycoplasma gallisepticum* str. F, ~~a~~ *Nitratifractor salsuginis* str DSM 16511, ~~a~~ *Parvibaculum lavamentivorans*, ~~a~~ *Roseburia intestinalis*, ~~a~~ *Neisseria cinerea*, ~~a~~ *Gluconacetobacter diazotrophicus*, ~~an~~ *Azospirillum* B510, ~~a~~ *Sphaerochaeta globus* str. Buddy, ~~a~~ *Flavobacterium columnare*, ~~a~~ *Fluviicola taffensis*, ~~a~~ *Bacteroides coprophilus*, ~~a~~ *Mycoplasma mobile*, ~~a~~ *Lactobacillus farciminis*, ~~a~~ *Streptococcus pasteurianus*, ~~a~~ *Lactobacillus johnsonii*, ~~a~~ *Staphylococcus pseudintermedius*, ~~a~~ *Filifactor alocis*, ~~a~~ *Treponema denticola*, ~~a~~ *Legionella pneumophila* str. Paris, ~~a~~ *Sutterella wadsworthensis*, ~~a~~ *Corynebacter diphtheriae*, ~~or a~~ *Streptococcus aureus* and ~~; a~~ *Francisella novicida* ~~(optionally a Francisella novicida Cpf1) or a Natronobacterium gregoryi Argonaute modified or repurposed to target RNA, wherein optionally the sgRNA 3' end or "scaffold sequence" comprises all or part of, or is derived from, the wild type (WT) cognate guide nucleic acid of each of these respective bacteria or archaeal organisms.~~

~~2.~~3. The engineered nucleoprotein complex of ~~Claim~~ claim 1 or 2, wherein the 5' ~~RNA-hybridizing or binding~~ end of the sgRNA is between about 15 to 25~~, or 20, 21, 22~~ nucleotides in length, and wherein the RNA sequence capable of binding to or associating with the nuclease-inactive RCas9~~Cas9~~ polypeptide is between about 85 and 100~~, or 90, 91, 92, 93, 94 or 95~~ nucleotides in length.~~,~~

4. The engineered nucleoprotein complex of any one of claims 1-3, wherein ~~and optionally~~ the ~~Cas9~~ nuclease-inactive RCas9 polypeptide ~~is adapted to be associated with, fused with, or that binds to or~~ is covalently or non-covalently linked to ~~,~~ an effector polypeptide, a targeting agent, an enzyme, ~~and/or~~ a detectable moiety~~, wherein optionally the effector polypeptide comprises~~ or an RNA modifying polypeptide. ~~,~~

~~wherein optionally the Cas9 polypeptide is a recombinant or synthetic polypeptide,~~

~~wherein optionally the target RNA is (or the RNA sequence that recognizes by hybridization, or hybridizes to or binds to, the target RNA, is antisense to:) a messenger RNA (mRNA), ribosomal RNA (rRNA), signal recognition particle RNA (SRP RNA), transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), antisense RNA (aRNA), long noncoding RNA (lncRNA), microRNA (miRNA), piwi-interacting RNA (piRNA), small interfering RNA (siRNA), short hairpin RNA (shRNA), retrotransposon RNA, viral genome RNA, or viral noncoding RNA.~~

~~3. The engineered nucleoprotein complex of any one of Claims 1 or 2, wherein said Cas9 polypeptide is noncovalently associated with said effector polypeptide, targeting agent, detectable moiety, or RNA modifying polypeptide.~~

~~4. The engineered nucleoprotein complex of any one of Claims 1 or 2, wherein said Cas9 polypeptide is fused to or covalently linked to said effector polypeptide, targeting agent, detectable moiety,~~

~~and optionally the effector polypeptide is or comprises an RNA modifying polypeptide, and optionally the targeting agent is or comprises: a cytoplasmic polyadenylation element binding protein (CPEB), a zinc finger binding protein (ZBP), TIA-1 (a 3'UTR mRNA binding protein), a PSF (a protein component of spliceosomes) or a DNA-binding domain (DBD) of PSF, fragile X mental retardation protein (FMRP), IGF II mRNA-binding protein (IMP) 1 (IMP1), IMP2, IMP3, a cytoskeleton binding protein, a transmembrane protein, or an engineered protein comprising a combination of domains of these aforementioned proteins to generate a combinatorial trafficking phenomena,~~

~~and optionally the enzyme is involved in the modification of synthesis of a compound, optionally wherein the compound is a polypeptide or a nucleic acid, and optionally the association of the Cas9 polypeptide on a target RNA creates a local accumulation of intermediate products in a biosynthetic pathway to amplify the production of a medically- or technologically-useful compound compared to free-floating biosynthetic enzymes.~~

5. The engineered nucleoprotein complex of ~~any one of C~~claims ~~1-~~4, wherein said RNA modifying polypeptide comprises a splicing factor or an RNA splicing domain, ~~optionally~~ a RBFOX2 domain-containing protein, a protein known to influence RNA

splicing, or an RNA cleaving domain ~~(endonuclease), optionally as~~and/or a PIN domain-containing protein.

6. The engineered nucleoprotein complex of claim 5, wherein the RNA cleaving domain comprises an endonuclease.

~~6. The engineered nucleoprotein complex of any one of Claims 1-5, wherein said Cas9 polypeptide is covalently bound to the single guide RNA (sgRNA) by the linker.~~

7. The engineered nucleoprotein complex of any one of ~~C~~claims 1-6, wherein the RNA sequence capable of binding to or associating with the nuclease-inactive RCas9 polypeptide of said ~~single guide RNA (~~sgRNA~~)~~ ~~carries extensions of, or~~ comprises~~,~~ a secondary RNA structure~~s in the 3' end scaffold sequence~~.

~~8. The engineered nucleoprotein complex of any one of Claims 1-7, wherein said single guide RNA (sgRNA) comprises one or more point mutations that improve expression levels of the single guide RNAs via removal of partial or full transcription termination sequences or sequences that destabilize sgRNAs after transcription via action of trans acting nucleases by at least about 5%, 10%, 15% or more.~~

~~9.~~8.The engineered nucleoprotein complex of any one of ~~Claims 1-8~~claims 1-7, wherein said ~~single guide RNA (~~sgRNA~~)~~ comprises one or more point mutations that remove a transcription termination sequence, or an alteration, ~~or~~ an additional nucleotide or chemical moiety at the 5' end which stabilizes said single guide RNA against degradation.

~~10. The engineered nucleoprotein complex of Claim 9, wherein said additional nucleotide or chemical moiety at the 5' end of said single guide RNA (sgRNA) is selected from the group consisting of 2'O-methyl, phosphorothioates, and thiophosphonoacetate linkages and bases, and optionally the alteration or additional chemical moiety for chemical stabilization comprises a 2' F, locked nucleic acid (LNA), a 2' O-methoyethyl, or a unlocked nucleic acid (UNA).~~

~~11. The engineered nucleoprotein complex of any one of Claims 1-10, wherein said single guide RNA comprises one or more methylphosphonate, thiophosponoaceteate, or phosphorothioate linkages, optionally that reduce RNA nuclease activity on the sgRNA by at least about 5%, 10%, 15% or more.~~

~~12. The engineered nucleoprotein complex of any one of Claims 1-11, wherein said single guide RNA (sgRNA) comprises an alteration or an additional nucleotide or chemical moiety at the 5' end which improves RNA targeting by at least about 5%, 10%, 15% or more.~~

~~13. The engineered nucleoprotein complex of any one of Claims 1-12, wherein said single guide RNA comprises 2'-fluorine, 2'O-methyl, and/or 2'-methoxyethyl base modifications in the spacer or scaffold region of the sgRNA to improve target recognition or reduce nuclease activity on the single guide RNA by at least about 5%, 10%, 15% or more.~~

~~14. The engineered nucleoprotein complex of any one of Claims 1-13, wherein said single guide RNA comprises sufficient sequence antisense to the target RNA to allow it to hybridize under physiological conditions to at least about 5%, 10%, 15%, or between about 5% and 20%, or more of the target RNA.~~

~~15.~~9. The engineered nucleoprotein complex of any one of ~~Claims 1-14~~claims 1-8, wherein said ~~single guide~~ sgRNA comprises a sequence that is ~~antisense to or~~ complementary to at least a portion of the target RNA, wherein said portion is ~~optionally at least about 5%, 10%, 15% or more of the target RNA, or~~ between about 5% and 20% ~~, or more~~ of the target RNA.

~~16. The engineered nucleoprotein complex of any one of Claims 1-15, further comprising a CRISPR-targeting RNA (crRNA) and a trans-activating cRNA (tracrRNA), wherein said Cas9 polypeptide is complexed with or linked to, or covalently or non-covalently associated with, the CRISPR-targeting RNA (crRNA) in combination with the trans-activating cRNA (tracrRNA).~~

~~17. The engineered nucleoprotein complex of any one of Claims 1-16, wherein said RNA modifying polypeptide is further complexed with, or is linked to covalently or non-covalently, an antisense oligonucleotide.~~

~~18. The engineered nucleoprotein complex of Claim 17, wherein said antisense oligonucleotide comprises at least one modified nucleotide.~~

~~19. The engineered nucleoprotein complex of Claim 18, wherein said at least one modified nucleotide is selected from the group consisting of 2'OMe RNA and 2'OMe DNA nucleotides.~~

~~20. The engineered nucleoprotein complex of any one of Claims 1-19, wherein said nucleoprotein complex further comprises a PAMmer oligonucleotide, and optionally the~~

~~PAMmer also carries a 5' overhang which is required to maintain target specificity conferred by the sgRNA.~~

~~21. The engineered nucleoprotein complex of Claim 20, wherein said PAMmer oligonucleotide comprises one or more modified bases or linkages.~~

~~22. The engineered nucleoprotein complex of Claim 21, wherein said one or more modified bases or linkages are selected from the group consisting of locked nucleic acids and nuclease stabilized linkages.~~

~~23. The engineered nucleoprotein complex of any one of Claims 1-22, wherein said engineered nucleoprotein complex is adapted to be delivered to the nucleus of a cell.~~

~~24.~~10. The engineered nucleoprotein complex of ~~Claim 23~~any one of claims 1-9, wherein said engineered nucleoprotein complex is adapted to be delivered to the nucleus of a cell, ~~co-exported with a target RNA out of said nucleus.~~

~~25.~~ ~~The engineered nucleoprotein complex of any one of Claims 23 or 24,~~ and wherein said nuclease-inactive RCas9~~Cas9~~ polypeptide ~~comprises, or further comprises, optionally~~ is covalently or non-covalently linked ~~fused or linked~~ to one or more of a nuclear localization signal, one or more linker peptide(s), one or more XTEN peptide(s), or ~~optionally,~~ an SV40 nuclear localization signal.

~~26. The engineered nucleoprotein complex of any one of Claims 1-25, wherein said Cas9 polypeptide is nuclease null.~~

~~27. The engineered nucleoprotein complex of any one of Claims 1-26, wherein said target RNA comprises a repeat sequence, and the 5' end RNA sequence that recognizes by hybridization (that hybridizes to or binds to) the target RNA comprises a sequence capable of hybridizing to, or is complementary to, the repeat sequence.~~

~~28. The engineered nucleoprotein complex of Claim 27, wherein said repeat sequence is selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof.~~

~~29. The engineered nucleoprotein complex of Claim 27 or 28, wherein said target RNA is associated with a disease or condition or infection, and optionally the disease or condition is caused by or is associated with a RNA microsatellite repeat expansion.~~

~~30. The engineered nucleoprotein complex of Claim 29, wherein said disease, condition, or infection is selected from the group consisting of myotonic dystrophy,~~

~~Huntington's disease, familial ALS, cancer, spinal muscular atrophy, spinocerebellar ataxia, Fragile X-associated tremor/ataxia syndrome, Spinal-bulbar muscular dystrophy, Oculopharyngeal muscular dystrophy, Fragile X syndrome , a viral or bacterial infection, wherein optionally the viral infection is a Herpesviridae or herpes simplex virus, a human immunodeficiency virus, Epstein Barr virus, hepatitis virus, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Zika virus, enteroviruses, Human Papillomavirus (HPV), influenza virus, Marburg virus, Ebola virus, Mumps virus, cytomegalovirus, rotavirus, Rubella virus, Varicella zoster virus, severe acute respiratory syndrome (SARS) coronavirus, a Paramyxoviridae or measles virus, West Nile virus, Yellow fever virus, or Dengue fever virus infection.~~

~~31. The engineered nucleoprotein complex of any of claims 1 to 30, wherein said Cas9 polypeptide is associated with an effector polypeptide, wherein the polypeptide is a toxic protein.~~

~~32.~~11. The engineered nucleoprotein complex of any of claims 1-10 ~~to 31~~, wherein said nuclease-inactive RCas9~~Cas9~~ polypeptide is ~~fused to, bound to, or~~ associated with an effector polypeptide, a targeting agent, an enzyme and/or a detectable agent or moiety, wherein ~~optionally~~ the nuclease-inactive RCas9~~Cas9~~ polypeptide is a recombinant or synthetic polypeptide.

~~33. The engineered nucleoprotein complex of Claim 32, wherein said detectable agent or moiety comprises a detectable polypeptide or composition which has been fused or linked to said Cas9 polypeptide.~~

~~34. The engineered nucleoprotein complex of Claim 33, wherein said detectable polypeptide comprises a polypeptide which is inactivated when said detectable polypeptide is in the nucleus of a cell.~~

~~35. The engineered nucleoprotein complex of Claim 34, wherein said detectable polypeptide is not detectable when said detectable polypeptide is in the nucleus of a cell but is detectable when said detectable polypeptide is not in the nucleus of the cell.~~

~~36. The engineered nucleoprotein complex of Claim 35, wherein said detectable polypeptide is detectable when it is not in the nucleus of the cell via an association with another agent which is detectable.~~

~~37. The engineered nucleoprotein complex of any one of Claims 32-36, wherein said detectable polypeptide is a fluorescent, split fluorescent, or luminescent polypeptide, or said detectable agent or moiety comprises a fluorescent, split fluorescent, or luminescent agent.~~

~~38. The engineered nucleoprotein complex of Claim 37 wherein said fluorescent polypeptide comprises or is a green fluorescent protein (GFP) or an enhanced GFP.~~

~~39. The engineered nucleoprotein complex of any one of Claims 1-38, wherein said single guide RNA (sgRNA) comprises one or more point mutations that improves expression levels of the single guide RNAs by at least 5%, 10%, 15% or more via removal of partial or full transcription termination sequences or sequences that destabilize single guide RNAs after transcription via action of trans-acting nucleases.~~

~~40. The engineered nucleoprotein complex of any one of Claims 1-39, wherein said Cas9 polypeptide is complexed with a CRISPR-targeting RNA (crRNA) in combination with a trans-activating cRNA (tracrRNA).~~

~~41. The engineered nucleoprotein complex of any one of Claims 1-40, wherein said Cas9 polypeptide is further complexed with an antisense oligonucleotide, wherein the antisense oligonucleotide comprises a PAMmer oligonucleotide which is complementary to a sequence in the target RNA.~~

~~42. The engineered nucleoprotein complex of Claim 41, wherein said PAMmer oligonucleotide comprises at least one modified nucleotide.~~

~~43. The engineered nucleoprotein complex of Claim 20, wherein said at least one modified nucleotide is selected from the group consisting of 2'OMe RNA and 2'OMe DNA nucleotides.~~

~~44. The engineered nucleoprotein complex of any one of Claims 1-43, wherein said Cas9 polypeptide is adapted to be delivered to the nucleus of a cell.~~

~~45. The engineered nucleoprotein complex of Claim 44, wherein said Cas9 polypeptide is adapted to be co-exported with a target RNA out of said nucleus.~~

12. A first nucleic acid encoding the nuclease-inactive RCas9 polypeptide as recited in any one of claims 1, 2, 4, 10 or 11 and a second nucleic acid encoding the sgRNA as recited in any one of claims 1, 3, 8 or 9.

13. A chimeric nucleic acid encoding the engineered nucleoprotein complex of any one of claims 1-11.

~~46. A vector comprising a nucleic acid, or nucleic acids, optionally vector or vectors, encoding the engineered nucleoprotein complex of any one of Claims 1-45, wherein optionally the vector is, comprises or is derived from an adenovirus, an adeno-associated virus (AAV), a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~47.~~14. A cell comprising~~, or having contained therein~~:

(a) the engineered nucleoprotein complex of any of claims 1-11~~45~~; or

(b) a nucleic acid of claim 12, or nucleic acid of claim 13,~~s, optionally vector or vectors, encoding the engineered nucleoprotein complex of any one of Claims 1-45,~~

wherein ~~optionally~~ the cell is a mammalian cell or a human cell.

~~48. A chimeric nucleic acid encoding the engineered nucleoprotein complex of any one of Claims 1-45, wherein optionally the nucleic acid is a recombinant or synthetic nucleic acid, wherein optionally the nucleic acid is operably linked to a constitutive or an inducible promoter.~~

~~49. The nucleic acid of Claim 48, wherein the expression of one or more of the Cas9 polypeptide, the sgRNA, the PAMmer oligonucleotide, the effector polypeptide, the detectable moiety, or combinations thereof, is controlled by a regulatable or constitutive promoter.~~

~~50. A vector comprising the nucleic acid of any of Claims 48 or 49, wherein optionally the vector is, comprises or is derived from an adenovirus, an adeno-associated virus (AAV), a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~51. A cell or tissue comprising: the engineered nucleoprotein complex of any one of Claims 1-45; the nucleic acid of Claims 48 or 49; or the vector of Claim 50.~~

~~52. A method of treating, preventing, ameliorating or reducing the symptoms of a disease or condition, or infection, in a mammalian or a human subject comprising administering to said mammalian or human subject:~~

~~(a) the engineered nucleoprotein complex of any of claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-~~

covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide; or

(b) a nucleic acid, or nucleic acids, optionally vector or vectors, encoding the engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide, and wherein the nucleic acid is, or nucleic acids are, expressed intracellularly and express the engineered nucleoprotein complex, (c) pharmaceutical composition comprising

(i) the engineered nucleoprotein complex of any of claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide; or

(ii) a nucleic acid, or nucleic acids, optionally vector or vectors, encoding the engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide,

and optionally an excipient,

and optionally the pharmaceutical compound is formulated for enteral or parenteral delivery, or for intravenous (IV) delivery; or

(d) a cell or tissue of claim 51;

thereby modifying an RNA in a cell and treating, preventing, or ameliorating or reducing the symptoms of the disease or condition, or infection,,

wherein optionally the engineered nucleoprotein complex or the nucleic acid or vector encoding the Cas9 polypeptide is carried or contained in a nanoparticle, a particle, a micelle or a liposome or lipoplex, a polymersome, a polyplex or a dendrimer, which optionally can further comprise or express a cell penetrating moiety or peptide.

53. The method of Claim 52, wherein the nucleic acid or nucleic acids encoding one or all of the components of the engineered nucleoprotein complex is/are carried by or is/are

~~contained in a single vector, or each component (the Cas9 polypeptide, the sgRNA, the effector polypeptide, or a combination of components, is carried by or is contained in a separate vector,~~

~~and optionally the vector or vectors are adenovirus vectors, or one or more adeno-associated virus (AAV) vectors, a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~54. The method of Claim 52 or 53, wherein the expression of one or more of the Cas9 polypeptide, the sgRNA, the PAMmer oligonucleotide, the effector polypeptide, , or combinations thereof is controlled by a regulatable or constitutive promoter.~~

~~55. The method of any of Claims 52-54, wherein the nucleic acid encoding the single guide RNA (sgRNA) is carried by or is contained in the same vector as the nucleic acid encoding the Cas9 polypeptide, optionally adenovirus or AAV vectors, a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~56. The method of any of Claims 52-55, wherein the nucleic acid encoding the sgRNA and the nucleic acid encoding the Cas9 polypeptide are carried by or is contained in different vectors, optionally adenovirus or AAV vectors, a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~57. The method of any of Claims 52-56 wherein the nucleic acid encoding the effector polypeptide, optionally a RNA modifying polypeptide, is carried by the same or is carried by or is contained in a separate vector, optionally an AAV vector, a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

~~58. The method of any one of Claims 52-57, wherein the disease or condition is caused by a repeat sequence selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof.~~

~~59. The method of Claim 52-58, wherein said disease, condition, or infection is caused by or is associated with a RNA microsatellite repeat expansion, or is selected from the group consisting of myotonic dystrophy, Huntington's disease, familial ALS, cancer, spinal muscular atrophy, spinocerebellar ataxia, Fragile X-associated tremor/ataxia syndrome, Spinal bulbar muscular dystrophy, Oculopharyngeal muscular dystrophy, Fragile X syndrome, a viral or bacterial infection, wherein optionally the viral infection is a Herpesviridae or herpes simplex virus, a human immunodeficiency virus, Epstein Barr virus,~~

hepatitis virus, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Zika virus, enteroviruses, Human Papillomavirus (HPV), influenza virus, Marburg virus, Ebola virus, Mumps virus, cytomegalovirus, rotavirus, Rubella virus, Varicella zoster virus, severe acute respiratory syndrome (SARS) coronavirus, a Paramyxoviridae or measles virus, West Nile virus, Yellow fever virus, or Dengue fever virus infection.

60. The method of any one of Claims 52-59, wherein the administration route is selected from the group consisting of oral, pulmonary, intraperitoneal (ip), intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, buccal, nasal, sublingual, ocular, rectal and vaginal.

61. A method of expressing the engineered nucleoprotein complex of any of claims 1-45, comprising introducing a vector of Claims 46 or 50 or a nucleic acid of claims 48 or 49 into a cell under conditions in which said cell expresses said nucleoprotein complex.

62. A method of tracking a target RNA or measuring the amount of a target RNA in a cell comprising administering to the cell engineered nucleoprotein complex of any of claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, a detectable moiety, and allowing the engineered nucleoprotein complex to bind to said target RNA in said cell and determining the location of said target RNA in said cell or determining the amount of said target RNA in said cell.

63. The method of Claim 61, wherein said engineered nucleoprotein complex binds to said target RNA in a nucleus of said cell and is subsequently co-exported from said nucleus with said target RNA.

64. The method of any one of Claims 63 or 64, wherein the location of said target RNA in said cell or the amount of said target RNA in said cell is determined using a fluorescence microscopy or equivalent thereof.

65. A method of modifying the amount or structure of a target RNA in a cell in vitro or in vivo comprising allowing an engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide, to bind to said target RNA in said cell under conditions in which the amount or structure of said target RNA in said cell is modified.

66. A method of modifying the amount or structure of a target RNA in a cell in vitro or in vivo comprising expressing one or more components of the engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide, in a cell under conditions in which the amount or structure of said target RNA in said cell is modified, wherein the one or more components of the engineered nucleoprotein complex comprises a Cas9 polypeptide, a sgRNA, a PAMmer oligonucleotide, an effector protein, a detectable moiety, or combinations thereof.

67. A method of measuring RNA content or dynamics in a sample, comprising: introducing the engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, a detectable moiety, into said sample; and

observing , detecting or measuring the amount of the detectable agent in said sample.

68. The method of Claim 67, comprising introducing a nucleic acid of Claims 48 or 49 or a vector of Claims 46 or 50 into said sample under conditions in which said Cas9 polypeptide is expressed.

69. The method of Claims 67 or 68, further comprising introducing a single guide RNA.

70. The method of any one of Claims 67-69, further comprising introducing a PAMmer oligonucleotide.

71. The method of any one of Claims 67-70, wherein said sample comprises or is derived from a tissue , a biopsy, a serum or blood sample, or a sputum sample.

72. The method of any one of Claims 67-71, wherein said sample comprises a plurality of cells.

73. The method of any one of Claims 67-72, comprising measuring the expression level or abundance of a target RNA in said sample.

74. The method of any one of Claims 67-73, comprising diagnosing a disease, condition, or infection of said sample, or in an individual from which said sample was derived, of said sample based on the expression level or abundance of said target RNA in said sample,

and optionally the target RNA is derived from a viral or bacterial infection, wherein optionally the viral infection is a Herpesviridae or herpes simplex virus, a human immunodeficiency virus, Epstein Barr virus, hepatitis virus, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Zika virus, enteroviruses, Human Papillomavirus (HPV), influenza virus, Marburg virus, Ebola virus, Mumps virus, cytomegalovirus, rotavirus, Rubella virus, Varicella zoster virus, severe acute respiratory syndrome (SARS) coronavirus, a Paramyxoviridae or measles virus, West Nile virus, Yellow fever virus, or Dengue fever virus infection..

75. The method of any one of Claims 67-74, wherein said target RNA comprises a repeat sequence.

76. The method of Claim 75, wherein said repeat sequence is selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof.

77. The method of Claim 75 or 76, wherein said repeat sequence is associated with a disease, condition, or infection.

78. The method of Claim 77, wherein said disease or condition is caused by or is associated with a RNA microsatellite repeat expansion, or is selected from the group consisting of myotonic dystrophy, Huntington's disease, familial ALS, cancer, spinal muscular atrophy, spinocerebellar ataxia, Fragile X-associated tremor/ataxia syndrome, Spinal bulbar muscular dystrophy, Oculopharyngeal muscular dystrophy, and Fragile X syndrome.

79. A method of modifying a target RNA in a sample, comprising:

introducing the engineered nucleoprotein complex of any one of Claims 1-44, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide, into said sample; and

modifying said target RNA in said sample using the RNA modifying polypeptide.

80. The method of Claim 79, comprising introducing a nucleic acid of Claim 45 or 49 or a vector of Claim 50 into said sample under conditions in which said Cas9 polypeptide is expressed.

81. The method of Claim 79 or 80, further comprising introducing a single guide RNA.

~~82. The method of any one of Claims 79-81, further comprising introducing a PAMmer oligonucleotide.~~

~~83. The method of any one of Claims 79-82, wherein said sample comprises a tissue.~~

~~84. The method of any one of Claims 79-83, wherein said sample comprises a plurality of cells.~~

~~85. The method of any one of Claims 79-84, comprising modifying the amount of target RNA in said sample.~~

~~86. The method of Claim 85, wherein said target RNA comprises a repeat sequence.~~

~~87. The method of Claim 86, wherein said repeat sequence is selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof.~~

~~88. The method of Claim 86 or 87, wherein said repeat sequence is associated with a disease.~~

~~89. The method of Claim 88, wherein said disease is caused by or is associated with a RNA microsatellite repeat expansion, or is selected from the group consisting of myotonic dystrophy, Huntington's disease, familial ALS, cancer, spinal muscular atrophy, spinocerebellar ataxia, Fragile X-associated tremor/ataxia syndrome, Spinal-bulbar muscular dystrophy, Oculopharyngeal muscular dystrophy, and Fragile X syndrome.~~

~~90.~~15. A pharmaceutical composition comprising

(a) the engineered nucleoprotein complex of any of claims 1-~~45~~11~~, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide~~; or

(b) a nucleic acid~~s~~ of claim 12, or the nucleic acid of claim 13~~s~~, ~~optionally vector or vectors, encoding the engineered nucleoprotein complex of any one of Claims 1-45, wherein said Cas9 polypeptide is adapted to be associated with, or that binds to or is covalently or non-covalently linked to, an effector polypeptide wherein optionally the effector polypeptide comprises an RNA modifying polypeptide,~~

~~and optionally an excipient,~~

~~and~~ wherein optionally the pharmaceutical compound is formulated for enteral or parenteral delivery, or for intravenous (IV) delivery.

~~91. The pharmaceutical composition of Claim 90, wherein the engineered nucleoprotein complex or the nucleic acid or vector encoding the nucleoprotein complex is carried in a nanoparticle, a particle, a micelle or a liposome or lipoplex, a polymersome, a polyplex or a dendrimer, which optionally can further comprise or express a cell penetrating moiety or peptide.~~

~~92. The pharmaceutical composition of Claim 91, wherein the nanoparticle or particle comprises lipids, polymers, hydrogel, or a combination thereof.~~

~~93. The pharmaceutical composition of any one of Claims 90-93, wherein the sgRNA is contained in the same vector as the Cas9 polypeptide, or is contained in a different vector as the Cas9 polypeptide.~~

~~94. The pharmaceutical composition of any one of Claims 90-94, wherein the nucleic acid encoding the Cas9 polypeptide and the nucleic acid encoding the sgRNA is carried in one or more vectors, optionally adenovirus vectors or adeno-associated virus (AAV) vectors, a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.~~

16. The engineered nucleoprotein complex of any one of claims 1-11, the nucleic acids of claim 12 or the nucleic acid of claim 13, the cell of claim 14, or the pharmaceutical composition of claim 15 for use in therapy.

17. Use of the engineered nucleoprotein complex of any one of claims 1-11, the nucleic acids of claim 12 or the nucleic acid of claim 13, the cell of claim 14, or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating, preventing, ameliorating or reducing a symptom of a disease or condition, or an infection, in a mammalian or a human subject.

18. The use of claim 16 or 17, wherein the disease or the condition is caused by a repeat sequence selected from the group consisting of CTG, CCTG, CAG, GGGGCC, and any combination thereof, and wherein the disease or the condition is caused by or associated with a RNA microsatellite repeat expansion.

19. The use according to any one of claims 16-18, wherein the engineered nucleoprotein complex, nucleic acid, cell or pharmaceutical composition is to be administered by a route selected from the group consisting of oral, pulmonary, intraperitoneal

(ip), intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, buccal, nasal, sublingual, ocular, rectal and vaginal.

95. A recombinant or synthetic Cas9 polypeptide,

wherein the Cas9 polypeptide:

(a) is a, or is derived from a, bacterial or archaeal Cas9 polypeptide; and

(b)

(i) lacks a domain, or a portion of a domain, of a corresponding wild type (WT) Cas9 polypeptide, wherein optionally the domain is an HNH and/or RuvC nuclease domain of Cas9, comprises a ββα metal fold comprising or including a Cas9 polypeptide active site, or combinations thereof;

(ii) lacks DNase, or DNA cleaving, capability or activity, or nickase activity, wherein optionally the DNase, or DNA cleaving capability or activity is removed by modification (mutation) or removal of all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide DNase active site or a ββα metal fold that comprising a Cas9 polypeptide active site, or combinations thereof,

(iii) lacks all or part of: an HNH and/or RuvC nuclease domain of Cas9, a Cas9 polypeptide DNase active site or a ββα-metal fold that comprising a Cas9 polypeptide active site, or combinations thereof, thereby optionallyreducing the size of the polypeptide, optionally facilitating packaging of a Cas9 coding nucleotide in a viral or other delivery vector, or

(iv) is a variant of a WT Cas9 polypeptide, and has one or more amino acid mutations that result in reduced DNase or nuclease activity relative to a corresponding WT Cas9 polypeptide,

and optionally the archaeal or bacterial Cas9 polypeptide is, comprises or is derived from: a *Haloferax mediteranii*, a *Mycobacterium tuberculosis*, a Francisella tularensis subsp. novicida, a Pasteurella multocida, a Neisseria meningitidis, a Campylobacter jejune, a Streptococcus thermophilus LMD-9 CRISPR 3, a Campylobacter lari CF89-12, a Mycoplasma gallisepticum str. F, a Nitratifractor salsuginis str DSM 16511, a Parvibaculum lavamentivorans, a Roseburia intestinalis, a Neisseria cinerea, a Gluconacetobacter diazotrophicus, an Azospirillum B510, a Sphaerochaeta globus str. Buddy, a Flavobacterium columnare, a Fluviicola taffensis, a Bacteroides coprophilus, a Mycoplasma mobile, a

~~Lactobacillus farciminis, a Streptococcus pasteurianus, a Lactobacillus johnsonii, a Staphylococcus pseudintermedius, a Filifactor alocis, a Treponema denticola, a Legionella pneumophila str. Paris, a Sutterella wadsworthensis, a Corynebacter diphtheriae, or a Streptococcus aureus; a Francisella novicida (optionally a Francisella novicida Cpf1) or a Natronobacterium gregoryi Argonaute modified or repurposed to target RNA,~~

~~wherein optionally the Cas9 polypeptide further comprises an sgRNA, wherein optionally the sgRNA comprises a "scaffold sequence" capable of binding to or associating with the Cas9 polypeptide comprising all or part of, or is derived from, the wild type (WT) cognate guide nucleic acid of the wild type (WT) bacteria or archaeal organism from which the Cas9 polypeptide was derived,~~

~~and optionally the sgRNA further comprises on its 5' end, an RNA sequence that recognizes by hybridization (that hybridizes to or binds to) a target RNA,~~

~~and optionally the Cas9 polypeptide is adapted to be associated with, fused to, or that binds to or is covalently or non-covalently linked to, an effector polypeptide, a targeting agent, an enzyme, and/or a detectable moiety, wherein optionally the effector polypeptide comprises an RNA modifying polypeptide.~~

~~96. A recombinant or synthetic nucleic acid encoding the Cas9 polypeptide of claim 95, wherein optionally the nucleic acid is a chimeric nucleic acids encoding the Cas9 polypeptide of claim 95 and an sgRNA.~~

20. A method of expressing the engineered nucleoprotein complex of any one of claims 1-11, comprising introducing the nucleic acids of claim 12 or the nucleic acid of claim 13 into a cell *in vitro* under conditions in which said cell expresses said nucleoprotein complex.

21. A vector comprising ~~or having contained therein~~ the nucleic acid~~s~~ claim of claim 12 or the nucleic acid of claim 13. ~~98,~~

22. The vector of claim 21, wherein the vector is a single vector.

23. The vector of claim 21 or 22, wherein the vector contains or carries the nucleic acid(s) encoding the engineered nucleoprotein complex or one or more components thereof; or wherein the vector contains or carries each component of the engineered nucleoprotein complex.

24. The vector of any one of claims 21-23, further comprising a regulatable or a constitutive promoter that regulates expression of one or more of the nuclease-inactive RCas9 polypeptide, the sgRNA, the effector polypeptide, or combinations thereof.

~~97.~~25. ~~wherein optionally t~~The vector of any one of claims 21-24 is, wherein the vector comprises or is derived from an adenovirus, an adeno-associated virus (AAV), a retrovirus, a herpes simplex virus, a human immunodeficiency virus (HIV), or a synthetic vector.

~~98. A cell or tissue comprising or having contained therein the Cas9 polypeptide of claim 95, or the nucleic acid of claim 96.~~