CLAIMS

1. A Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Cas complex, comprising:
   (1) an RNA guide sequence comprising a spacer sequence capable of hybridizing to a target RNA, and a direct repeat (DR) sequence 3' to the spacer sequence; and,
   (2) a CRISPR-associated protein (Cas) having an amino acid sequence of any one of SEQ ID NOs: 1-7, or a derivative or functional fragment of said Cas;
   wherein the Cas, the derivative, and the functional fragment of said Cas, are capable of (i) binding to the RNA guide sequence and (ii) targeting the target RNA,
   with the proviso that the spacer sequence is not 100% complementary to a naturally-occurring bacterialphage nucleic acid when the complex comprises the Cas of any one of SEQ ID NOs: 1-7.
2. The CRISPR-Cas complex of claim 1, wherein the DR sequence has substantially the same secondary structure as the secondary structure of any one of SEQ ID NOs: 8-14.
3. The CRISPR-Cas complex of claim 1, wherein the DR sequence is encoded by any one of SEQ ID NOs: 8-14.
4. The CRISPR-Cas complex of claim 1, 2, or 3, wherein the target RNA is encoded by a eukaryotic DNA.
5. The CRISPR-Cas complex of claim 4, wherein the eukaryotic DNA is a non-human mammalian DNA, a non-human primate DNA, a human DNA, a plant DNA, an insect DNA, a bird DNA, a reptile DNA, a rodent DNA, a fish DNA, a worm / nematode DNA, a yeast DNA.
6. The CRISPR-Cas complex of any one of claims 1-5, wherein the target RNA is an mRNA.
7. The CRISPR-Cas complex of any one of claims 1-6, wherein the spacer sequence is between 15-60 nucleotides, between 25-50 nucleotides, or about 30 nucleotides.
8. The CRISPR-Cas complex of any one of claims 1-7, wherein the spacer sequence is 90-100% complementary to the target RNA.

9. The CRISPR-Cas complex of any one of claims 1-8, wherein the derivative comprises conserved amino acid substitutions of one or more residues of any one of SEQ ID NOs: 1-7.

10. The CRISPR-Cas complex of claim 9, wherein the derivative comprises only conserved amino acid substitutions.

11. The CRISPR-Cas complex of any one of claims 1-10, wherein the derivative has identical sequence to wild-type Cas of any one of SEQ ID NOs: 1-7 in the HEPN domain or the RXXXXH motif.

12. The CRISPR-Cas complex of any one of claims 1-9, wherein the derivative is capable of binding to the RNA guide sequence hybridized to the target RNA, but has no RNase catalytic activity due to a mutation in the RNase catalytic site of the Cas.

13. The CRISPR-Cas complex of claim 12, wherein the derivative has an N-terminal deletion of no more than 210 residues, and/or a C-terminal deletion of no more than 180 residues.

14. The CRISPR-Cas complex of claim 13, wherein the derivative has an N-terminal deletion of about 180 residues, and/or a C-terminal deletion of about 150 residues.

15. The CRISPR-Cas complex of any one of claims 12-14, wherein the derivative further comprises an RNA base-editing domain.

16. The CRISPR-Cas complex of claim 15, wherein the RNA base-editing domain is an adenosine deaminase, such as a double-stranded RNA-specific adenosine deaminase (*e.g.*, ADAR1 or ADAR2); apolipoprotein B mRNA editing enzyme; catalytic polypeptide-like (APOBEC); or activation-induced cytidine deaminase (AID).

17. The CRISPR-Cas complex of claim 16, wherein the ADAR2 has E488Q/T375G double mutation or is ADAR2DD.

18. The CRISPR-Cas complex of any one of claims 15-17, wherein the base-editing domain is further fused to an RNA-binding domain, such as MS2.

19. The CRISPR-Cas complex of any one of claims 12-14, wherein the derivative further comprises an RNA methyltransferase, a RNA demethylase, an RNA splicing modifier, a localization factor, or a translation modification factor.

20. The CRISPR-Cas complex of any one of claims 1-19, wherein the Cas, the derivative, or the functional fragment comprises a nuclear localization signal (NLS) sequence or a nuclear export signal (NES).

21. The CRISPR-Cas complex of any one of claims 1-20, wherein targeting of the target RNA results in a modification of the target RNA.

22. The CRISPR-Cas complex of claim 21, wherein the modification of the target RNA is a cleavage of the target RNA.

23. The CRISPR-Cas complex of claim 21, wherein the modification of the target RNA is deamination of an adenosine (A) to an inosine (I).

24. The CRISPR-Cas complex of any one of claims 1-23, further comprising a target RNA comprising a sequence capable of hybridizing to the spacer sequence.

25. A fusion protein, comprising (1) the Cas, the derivative thereof, or the functional fragment thereof, of any one of claims 1-24, and (2) a heterologous functional domain.

26. The fusion protein of claim 25, wherein the heterologous functional domain comprises: a nuclear localization signal (NLS), a reporter protein or a detection label (*e.g.*, GST, HRP, CAT, GFP, HcRed, DsRed, CFP, YFP, BFP), a localization signal, a protein targeting moiety, a DNA binding domain (*e.g.*, MBP, Lex A DBD, Gal4 DBD), an epitope tag (*e.g.*, His, myc, V5, FLAG, HA, VSV-G, Trx, *etc*), a transcription activation domain (*e.g.*, VP64 or VPR), a transcription inhibition domain (*e.g.*, KRAB moiety or SID moiety), a nuclease (*e.g.*, FokI), a deamination domain (*e.g.*, ADAR1, ADAR2, APOBEC, AID, or TAD), a methylase, a demethylase, a transcription release factor, an HDAC, a polypeptide having ssRNA cleavage activity, a polypeptide having dsRNA cleavage activity, a polypeptide having ssDNA cleavage activity, a polypeptide having dsDNA cleavage activity, a DNA or RNA ligase, or any combination thereof.

27. The fusion protein of claim 25 or 26, wherein the heterologous functional domain is fused N-terminally, C-terminally, or internally in the fusion protein.

28. A conjugate, comprising (1) the Cas, the derivative thereof, or the functional fragment thereof, of any one of claims 1-24, conjugated to (2) a heterologous functional moiety.

29. The conjugate of claim 28, wherein the heterologous functional moiety comprises: a nuclear localization signal (NLS), a reporter protein or a detection label (*e.g.*, GST, HRP, CAT, GFP, HcRed, DsRed, CFP, YFP, BFP), a localization signal, a protein targeting moiety, a DNA binding domain (*e.g.*, MBP, Lex A DBD, Gal4 DBD), an epitope tag (*e.g.*, His, myc, V5, FLAG, HA, VSV-G, Trx, *etc*), a transcription activation domain (*e.g.*, VP64 or VPR), a transcription inhibition domain (*e.g.*, KRAB moiety or SID moiety), a nuclease (*e.g.*, FokI), a deamination domain (*e.g.*, ADAR1, ADAR2, APOBEC, AID, or TAD), a methylase, a demethylase, a transcription release factor, an HDAC, a polypeptide having ssRNA cleavage activity, a polypeptide having dsRNA cleavage activity, a polypeptide having ssDNA cleavage activity, a polypeptide having dsDNA cleavage activity, a DNA or RNA ligase, or any combination thereof.

30. The conjugate of claim 28 or 29, wherein the heterologous functional moiety is conjugated N-terminally, C-terminally, or internally with respect to the Cas, the derivative thereof, or the functional fragment thereof.

31. A polynucleotide encoding any one of SEQ ID NOs: 1-7, or a derivative thereof, or a functional fragment thereof, or a fusion protein thereof, provided that the polynucleotide is not any one of SEQ ID NOs: 15-21.

32. The polynucleotide of claim 31, which is codon-optimized for expression in a cell.

33. The polynucleotide of claim 32, wherein the cell is a eukaryotic cell.

34. A non-naturally occurring polynucleotide comprising a derivative of any one of SEQ ID NOs: 8-14, wherein said derivative (i) has one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10) nucleotides additions, deletions, or substitutions compared to any one of SEQ ID NOs: 8-14; (ii) has at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 97% sequence identity to any one of SEQ ID NOs: 8-14; (iii) hybridize under stringent conditions with any one of SEQ ID NOs: 8-14 or any of (i) and (ii); or (iv) is a complement of any of (i) - (iii), provided that the derivative is not any one of SEQ ID NOs: 8-14, and that the derivative encodes an RNA (or is an RNA) that has maintained substantially the same secondary structure as any of the RNA encoded by SEQ ID NOs: 8-14.

35. The non-naturally occurring polynucleotide of claim 34, wherein the derivative functions

as a DR sequence for any one of the Cas, the derivative thereof, or the functional fragment thereof, of any one of claims 1-24.

36. A vector comprising the polynucleotide of any one of claims 31-35.

37. The vector of claim 36, wherein the polynucleotide is operably linked to a promoter and optionally an enhancer.

38. The vector of claim 37, wherein the promoter is a constitutive promoter, an inducible promoter, a ubiquitous promoter, or a tissue specific promoter.

39. The vector of any one of claims 36-38, which is a plasmid.

40. The vector of any one of claims 36-38, which is a retroviral vector, a phage vector, an adenoviral vector, a herpes simplex viral (HSV) vector, an AAV vector, or a lentiviral vector.

41. The vector of claim 40, wherein the AAV vector is a recombinant AAV vector of the serotype AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAVrh74, AAV8, AAV9, AAV10, AAV 11, AAV 12, or AAV 13.

42. A delivery system comprising (1) a delivery vehicle, and (2) the CRISPR-Cas complex of any one of claims 1-24, the fusion protein of any one of claims 25-27, the conjugate of any one of claims 28-30, the polynucleotide of any one of claims 31-33, or the vector of any one of claims 36-41.

43. The delivery system of claim 42, wherein the delivery vehicle is a nanoparticle, a liposome, an exosome, a microvesicle, or a gene-gun.

44. A cell or a progeny thereof, comprising the CRISPR-Cas complex of any one of claims 1-24, the fusion protein of any one of claims 25-27, the conjugate of any one of claims 28-30, the polynucleotide of any one of claims 31-33, or the vector of any one of claims 36-41.

45. The cell or progeny thereof of claim 44, which is a eukaryotic cell (*e.g.*, a non-human mammalian cell, a human cell, or a plant cell) or a prokaryotic cell (*e.g.*, a bacteria cell).

46. A non-human multicellular eukaryote comprising the cell of claim 44 or 45.

47. The non-human multicellular eukaryote of claim 46, which is an animal (*e.g.*, rodent or primate) model for a human genetic disorder.

48. A method of modifying a target RNA, the method comprising contacting the target RNA with the CRISPR-Cas complex of any one of claims 1-24, wherein the spacer sequence is complementary to at least 15 nucleotides of the target RNA; wherein the Cas, the derivative, or the functional fragment associates with the RNA guide sequence to form the complex; wherein the complex binds to the target RNA; and wherein upon binding of the complex to the target RNA, the Cas, the derivative, or the functional fragment modifies the target RNA.

49. The method of claim 48, wherein the target RNA is modified by cleavage by the Cas.

50. The method of claim 48, wherein the target RNA is modified by deamination by a derivative comprising a Double-stranded RNA-specific adenosine deaminase.

51. The method of any one of claim 48-50, wherein the target RNA is an mRNA, a tRNA, an rRNA, a non-coding RNA, an lncRNA, or a nuclear RNA.

52. The method of any one of claims 48-51, wherein upon binding of the complex to the target RNA, the Cas, the derivative, and the functional fragment does not exhibit substantial (or detectable) collateral RNase activity.

53. The method of any one of claims 48-52, wherein the target RNA is within a cell.

54. The method of claim 53, wherein the cell is a cancer cell.

55. The method of claim 53, wherein the cell is infected with an infectious agent.

56. The method of claim 55, wherein the infectious agent is a virus, a prion, a protozoan, a fungus, or a parasite.

57. The method of any one of claims 53-56, wherein the CRISPR-Cas complex is encoded by a first polynucleotide encoding any one of SEQ ID NOs: 1-7, or a derivative or functional fragment thereof, and a second polynucleotide comprising any one of SEQ ID NOs: 8-14 and a sequence encoding a spacer RNA capable of binding to the target RNA, wherein the first and the second polynucleotides are introduced into the cell.

58. The method of claim 57, wherein the first and the second polynucleotides are introduced into the cell by the same vector.

59. The method of any one of claims 53-58, which cases one or more of: (i) *in vitro* or *in vivo* induction of cellular senescence; (ii) *in vitro* or *in vivo* cell cycle arrest; (iii) *in vitro* or *in vivo* cell growth inhibition and/or cell growth inhibition; (iv) *in vitro* or *in vitro* induction of anergy; (v) *in vitro* or *in vitro* induction of apoptosis; and (vi) *in vitro* or *in vitro* induction of necrosis.

60. A method of treating a condition or disease in a subject in need thereof, the method comprising administering to the subject a composition comprising the CRISPR-Cas complex of any one of claims 1-24 or a polynucleotide encoding the same; wherein the spacer sequence is complementary to at least 15 nucleotides of a target RNA associated with the condition or disease; wherein the Cas, the derivative, or the functional fragment associates with the RNA guide sequence to form the complex; wherein the complex binds to the target RNA; and wherein upon binding of the complex to the target RNA, the Cas, the derivative or the functional fragment cleaves the target RNA, thereby treating the condition or disease in the subject.

61. The method of claim 60, wherein the condition or disease is a cancer or an infectious disease.

62. The method of claim 61, wherein the cancer is Wilms' tumor, Ewing sarcoma, a neuroendocrine tumor, a glioblastoma, a neuroblastoma, a melanoma, skin cancer, breast cancer, colon cancer, rectal cancer, prostate cancer, liver cancer, renal cancer, pancreatic cancer, lung cancer, biliary cancer, cervical cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, medullary thyroid carcinoma, ovarian cancer, glioma, lymphoma, leukemia, myeloma, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or urinary bladder cancer.

63. The method of any one of claims 60-62, which is an *in vitro* method, an *in vivo* method, or an *ex vivo* method.

64. A cell or a progeny thereof, obtained by the method of any one of claims 48-59, wherein

the cell and the progeny comprises a non-naturally existing modification (*e.g.*, a non-naturally existing modification in a transcribed RNA of the cell / progeny).

65. A method to detect the presence of a target RNA, the method comprising contacting the target RNA with a composition comprising a fusion protein of any one of claims 25-27, or a conjugate of any one of claims 28-30, or a polynucleotide encoding the fusion protein, wherein the fusion protein or the conjugate comprises a detectable label (*e.g.*, one that can be detected by fluorescence, Northern blot, or FISH) and a complexed spacer sequence capable of binding to the target RNA.

66. A eukaryotic cell comprising a Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Cas complex, said CRISPR-Cas complex comprising:

(1) an RNA guide sequence comprising a spacer sequence capable of hybridizing to a target RNA, and a direct repeat (DR) sequence 3' to the spacer sequence; and,

(2) a CRISPR-associated protein (Cas) having an amino acid sequence of any one of SEQ ID NOs: 1-7, or a derivative or functional fragment of said Cas;

wherein the Cas, the derivative, and the functional fragment of said Cas, are capable of (i) binding to the RNA guide sequence and (ii) targeting the target RNA.