CLAIMS

1. Use of a non-naturally occurring nuclease system comprising one or more vectors comprising:

i) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule in a cell of a subject, and wherein the DNA molecule encodes one or more oncogene products expressed in the cell; and

ii) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

in the manufacture of a medicament for the prevention, inhibition, or treatment of cancer in a subject in need thereof, wherein components (i) and (ii) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule to alter expression of the one or more gene products.

2. An *in vitro* method of altering expression of one or more gene products in a cell, wherein the cell comprises a DNA molecule encoding the one or more gene products, the method comprising introducing into the cell:

(i)a non-naturally occurring nuclease system comprising one or more vectors comprising:

a) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of the DNA molecule; and

b) a regulatory element operable in the cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

wherein components (a) and (b) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule to alter expression of the one or more gene products.

3. The use of claim 1 or the method of claim 2, further comprising the step of providing a recombinant adeno-associated virus-packaging adenovirus (Ad-rAAVpack).

4. The use or method of claim 3, wherein the Ad-rAAVpack is provided concurrently or co-administered with the nuclease system.

5. The use of claim 1 or the method of claim 2, wherein the system is CRISPR-Cas9.

6. The use of claim 1 or the method of claim 2, wherein the system is packaged into a single adeno-associated virus (AAV) particle.

7. The use of claim 1 or the method of claim 2, wherein the adeno-associated virus-packaging adenovirus comprises at least one deletion in an adenoviral gene.

8. The use or method of claim 7, wherein the adeno-associated virus-packaging adenovirus is selected from adenovirus serotype 2, adenovirus serotype 5, or adenovirus serotype 35.

9. The use or method of claim 7 or claim 8, wherein the adenoviral gene is selected from El A, E1B, E2A, E2B, E3, E4, LI, L2, L3, L4, or L5.

10. The use of claim 1 or the method of claim 2, wherein the system inactivates one or more gene products.

11. The use of claim 1 or the method of claim 2, wherein the nuclease system excises at least one gene mutation.

12. The use of claim 1 or the method of claim 2, wherein the promoter is a H1 promoter.

13. The use or method of claim 12, wherein the H1 promoter is bidirectional.

14. The use or method of claim 13, wherein the H1 promoter comprises:

a) control elements that provide for transcription in one direction of the at least one nucleotide sequence encoding the gRNA; and

b) control elements that provide for transcription in the opposite direction of the nucleotide sequence encoding the genome-targeted nuclease.

15. The use of claim 1 or the method of claim 2, wherein the genome-targeted nuclease is Cas9 protein.

16. The use or method of claim 15, wherein the Cas9 protein is codon optimized for expression in the cell.

17. The use or method of any one of claims 12-14, wherein the promoter is operably linked to at least one, two, three, four, five, six, seven, eight, nine, or ten gRNA.

18. The use of claim 1 or the method of claim 2, wherein the target sequence is an oncogene or tumor suppressor gene.

19. The use of claim 1 or the method of claim 2, wherein the target sequence is an oncogene comprising at least one mutation.

20. The use or method of claim 19, wherein the target sequence is an oncogene selected from KRAS, PIK3CA, or IDHl .

21. The use or method of claim 20, wherein the target sequence is an oncogene, said oncogene is KRAS.

22. The use or method of claim 21, wherein the KRAS comprises a mutation selected from G13D, G12C, or G12D.

23. The use or method of claim 21 or claim 22, wherein the target sequence is selected from the group consisting of SEQ ID NO: 12-14, or combinations thereof.

24. The use or method of claim 20, wherein the target sequence is an oncogene, said oncogene is PIK3CA.

25. The use or method of claim 24, wherein the PIK3CA comprises a mutation selected from E345K, D549N, or H1047R.

26. The use or method of claim 24 or claim 25, wherein the target sequence is selected from the group consisting of SEQ ID NO: 16-18, or combinations thereof.

27. The use or method of claim 20, wherein the target sequence is an oncogene, said oncogene IDH1.

28. The use or method of claim 27, wherein the IDH1 comprises a R132H mutation.

29. The use of claim 1, wherein the gRNA sequence is selected from the group consisting of the nucleotide sequences set forth in SEQ ID NO: 1-10, or combinations thereof.

30. A non-naturally occurring nuclease system comprising one or more vectors comprising:

i) a promoter operably linked to at least one nucleotide sequence encoding a nuclease system guide RNA (gRNA), wherein the gRNA hybridizes with a target sequence of a DNA molecule in a cell of a subject, and wherein the DNA molecule encodes one or more oncogene products expressed in the cell; and

ii) a regulatory element operable in a cell operably linked to a nucleotide sequence encoding a genome-targeted nuclease,

for use in the prevention, inhibition, or treatment of cancer in a subject in need thereof, wherein components (i) and (ii) are located on the same or different vectors of the system, wherein the gRNA targets and hybridizes with the target sequence and the nuclease cleaves one or both strands of the DNA molecule to alter expression of the one or more gene products.