CLAIMS

1. A composition comprising a chimeric nuclease, wherein the chimeric nuclease comprises:

   (a) an I-TEVI nuclease domain, wherein the I-TEVI nuclease domain comprises a mutation at any one of positions corresponding to T11, V16, N14, E25, K26, R27, E36, K37, G38, C39, S41, L45, F49, I60, and E81 of SEQ ID NO: 700, or a combination thereof;

   (b) an RNA-guided nuclease Cas domain; and

   (c) a guide RNA, wherein the guide RNA comprises a nucleic acid sequence that targets an oncogenic mutation, wherein the oncogenic mutation is

      (i) an insertion of one or more nucleotides;

      (ii) a substitution or deletion of 10 or less nucleotides; or

      (iii) a single nucleotide polymorphism.

2. The composition of claim 1, wherein the I-TEVI nuclease domain comprises a mutation selected from a mutation corresponding to any one of T11V, V16I, N14G, E25D, K26R, R27A, E36S, K37N, G38N, C39V, S41H, L45F, F49Y, I60V, E81I, or a combination thereof.

3. The composition of claim 1, wherein the oncogenic mutation is an oncogenic mutation to a gene selected from any one of EGFR, Muc4, PIK3CA, KRAS, or a combination thereof.

4. The composition of claim 1, wherein the oncogenic mutation is not a deletion in exon 19 of EGFR.

5. The composition of claim 1, wherein a sequence comprising the oncogenic mutation is selected from a mutation set forth in any one of SEQ ID NOs: 1-683.

6. The composition of claim 1, wherein the oncogenic mutation comprises a mutation corresponding to an EGFR L858R mutation or an EGFR V769_D770insASV mutation.

7. The composition of claim 1, wherein the guide RNA hybridizes to a target nucleotide sequence set forth in SEQ ID NOs: 45, 130, or 141, or comprises a nucleotide sequence as set forth in SEQ ID NOs: 1045, 1130, 1141, or 1686.

8. The composition of claim 1, wherein the guide RNA hybridizes to a target nucleotide sequence set forth in SEQ ID NO: 683, or comprises a nucleotide sequence as set forth in SEQ ID NOs: 1683 or 1684.

9. The composition of claim 1, further comprising a linker that is operably linked to the I-TEVI nuclease domain and the RNA-guided nuclease Cas domain.

10. The composition of claim 1, wherein the RNA-guided nuclease Cas domain is an RNA-guided nuclease Cas9 domain.

11. The composition of claim 10, wherein the RNA-guided nuclease Cas9 domain is any one of an RNA-guided nuclease *Staphylococcus aureus* Cas9 domain, an RNA-guided nuclease *Streptococcus pyogenes* Cas9 domain, an RNA-guided nuclease *Neisseria meningitidis* Cas9 domain, an RNA-guided nuclease *Campylobacter jejuni* Cas9 domain, an RNA-guided nuclease *Streptococcus pasteurianus* Cas9 domain, an RNA-guided nuclease *Streptococcus pasteurianus* Cas9 domain, an RNA-guided nuclease *Clostridium cellulolyticum* Cas9 domain, or an RNA-guided nuclease *Geobacillus thermodenitrificans T1* Cas9 domain.

12. The composition of claim 10, wherein the RNA-guided nuclease *Staphylococcus aureus* Cas9 domain comprises a mutation corresponding to the D10E mutation.

13. The composition of claim 1, wherein the I-TEVI nuclease domain comprises an amino acid sequence that is at least 85%, 90%, 95%, 97%, 98%, or 99% identical to SEQ ID NO: 700.

14. The composition of claim 1, wherein the composition further comprises a donor nucleic acid.

15. The composition of claim 1, wherein the donor nucleic acid restores a non-oncogenic function of a gene comprising the oncogenic mutation.

16. A nucleic acid or plurality of nucleic acids encoding the chimeric nuclease or the guide RNA of claim 1, optionally further comprising a donor nucleic acid portion.

17. The nucleic acid or plurality of nucleic acids of claim 16, wherein the nucleic acid is an expression vector selected from a plasmid, a lentivirus vector, an adeno associated virus vector, or an adenovirus vector.

18. A method of silencing or disrupting at least a portion of the oncogenic mutation in a cell comprising contacting the composition of claim 1 to the cell.

19. A method of replacing at least a portion of the oncogenic mutation in a cell comprising contacting the composition of claim 16 to the cell.

20. The composition of claim 1 for use in a method of treating cancer in an individual in need thereof.