The Claims defining the Invention are as follows:

1. A method for reducing binding and/or cleavage of an off-target nucleic acid by a complex comprising a catalytically active Cas9 protein and a guide polynucleotide, the method comprising:

(a) contacting a first complex with a selected target nucleic acid, wherein the first complex comprises: (i) a catalytically active Cas9 protein, and (ii) a first guide polynucleotide that comprises a spacer adapted to bind to the selected target nucleic acid; and

(b) contacting a second complex with an off-target nucleic acid, wherein the second complex comprises (i) a catalytically inactive Cas9 protein (dCas9 protein) that does not cleave the off-target nucleic acid, and (ii) a second guide polynucleotide that comprises a spacer adapted to bind to the off-target nucleic acid,

thereby reducing binding and/or cleavage by the first complex of the off-target nucleic acid, and

wherein the method is not performed on a human or animal body.

2. The method of claim 1, wherein the guide polynucleotide is a single-guide RNA (sgRNA).

3. The method of claim 1 or claim 2, wherein the catalytically active Cas9 protein is a *S. pyogenes* Cas9 protein or an orthologous Cas9 protein.

4. The method of any preceding claim, wherein the dCas9 protein is a catalytically inactive *S. pyogenes* Cas9 protein or an orthologous Cas9 protein that is catalytically inactive.

5. The method of claim 4, wherein the dCas9 protein comprises one or more mutations in a RuvC-1 domain and one or more mutations in a HNH domain.

6. The method of any preceding claim, wherein the selected target nucleic acid is cleaved to provide a cleavage site, and the method further comprises modifying the target nucleic acid.

7. The method of claim 6, wherein the modifying comprises inserting at least a portion of a donor polynucleotide at the cleavage site.

8. The method of claim 6, wherein the modifying comprises deleting one or more nucleotides at the cleavage site.

9. The method of any preceding claim, wherein the method is performed in a cell.

10. The method of claim 9, wherein the first complex and the second complex are introduced into the cell by a method selected from the group consisting of transfection, transduction, electroporation, micelles and liposome delivery, lipid nanoparticles, viral delivery, and protein injection.

11. The method of claim 9 or claim 10, wherein the cell is a eukaryotic cell.

12. The method of any one of claims 1 to 8, wherein the method is performed *in vitro*.

13. The method of any preceding claim, wherein the selected target nucleic acid is DNA.

14. The method of claim 13, wherein the selected target nucleic acid is double-stranded DNA.