CLAIMS

What is claimed is:

1. A composition comprising a supercharged protein associated with an RNA-programmable nuclease, and wherein the composition further comprises a guide RNA associated with the RNA-programmable nuclease,

wherein the supercharged protein has an overall positive charge of at least +15 at pH 7.4, and wherein the supercharged protein has an overall positive charge that is at least +5 greater than its corresponding unmodified protein and is in sufficient quantity and is formulated for penetration into a cell.

2. The composition of claim 1, wherein the RNA-programmable nuclease is a Cas9 nuclease.

3. The composition of any one of claims 1-2, wherein the RNA-programmable nuclease specifically binds and cleaves a nucleic acid sequence.

4. The composition of claim 3, wherein the nucleic acid sequence is comprised in a gene or allele associated with a disease or disorder.

5. The composition of claim 3 or 4, wherein the guide RNA comprises a sequence identical or homologous to the nucleic acid sequence bound and cleaved by the nuclease.

6. The composition of any one of claims 3-5, wherein the nucleic acid sequence is a sequence comprised in a gene that is a therapeutic target.

7. The composition of claim 6, wherein the gene is a gene controlling cell fate.

8. The composition of claim 7, wherein the gene is a gene that induces or inhibits cellular programming towards a brown adipocyte cell fate.

9. The composition of claim 7 or 8, wherein the gene is PRDM16 or PPARγ.

10. The composition of any one of claims 1-9, wherein the supercharged protein is associated with the RNA-programmable nuclease via a covalent bond, thus forming a fusion protein.

11. The composition of any one of claims 1-10, wherein the supercharged protein is associated with the RNA-programmable nuclease via a linker.

12. The composition of claim 11, wherein the linker is a cleavable linker.

13. The composition of claim 12, wherein the linker is a UV-cleavable linker or a linker that is cleaved by a lysosomal enzyme.

14. The composition of any one of claims 1-9, wherein the supercharged protein is associated with the RNA-programmable nuclease via non-covalent interactions, thus forming a complex.

15. The composition of claim 14, wherein the supercharged protein has an overall net positive charge of at least +20 at pH 7.4.

16. The composition of claim 14, wherein the supercharged protein has an overall net positive charge of at least +25 at pH 7.4.

17. The composition of claim 14, wherein the supercharged protein has an overall net positive charge of at least +30 at pH 7.4.

18. The composition of claim 14, wherein the supercharged protein has overall net positive charge of at least +35 at pH 7.4.

19. The composition of claim 14, wherein the overall net positive charge of the complex is about +40.

20. The composition of any one of claims 1-19, wherein the supercharged protein is at least +10 more positively charged at pH 7.4 than its corresponding unmodified protein.

21. The composition of any one of claims 1-19, wherein the supercharged protein is at least +15 more positively charged at pH 7.4 than its corresponding unmodified protein.

22. The composition of any one of claims 1-21, wherein the supercharged protein is a fluorescent protein.

23. The composition of any one of claims 1-22, wherein the supercharged protein is green fluorescent protein (GFP).

24. The composition of any one of claims 1-23, wherein the supercharged protein is a superpositively charged GFP.

25. The composition of any one of claims 1-24, wherein the supercharged protein is a superpositively charged GFP comprising at least 20 contiguous amino acid residues of the sequence:
GGASKGERLFRGKVPILVELKGDVNGHKFSVRGKGKGDATRGKLTLKFICTTGKLPVPW PTLVTTLTYGVQCFSRYPKHMKRHDFFKSAMPKGYVQERTISFKKDGKYKTRAEVKFEG RTLVNRIKLKGRDFKEKGNILGHKLRYNFNSHKVYITADKRKNGIKAKFKIRHNVKDGSV QLADHYQQNTPIGRGPVLLPRNHYLSTRSKLSKDPKEKRDHMVLLEFVTAAGIKHGRDE RYK (SEQ ID NO: 1).

26. The composition of claim 25, wherein the supercharged protein comprises or consists of the amino acid sequence set forth in SEQ ID NO: 1.

27. The compositions of any one of claims 1-26, wherein the composition is a pharmaceutical composition.

28. The pharmaceutical composition of claim 27, wherein the composition comprises a pharmaceutically acceptable excipient.

29. The pharmaceutical composition of claim 27 or 28, wherein the composition is formulated for administration to a subject and comprises the supercharged protein and the RNA-

programmable nuclease in an amount effective for delivery to at least one cell of the subject.

30. The pharmaceutical composition of any one of claims 27-29, wherein the composition comprises the supercharged protein and the RNA-programmable nuclease in an amount effective for inducing a measurable therapeutic effect after administration to a subject.

31. Use of composition of any one of claims 1-26 or pharmaceutical composition of any one of claims 27-30 in the manufacture of a medicament for the treatment of genetic disease, optionally wherein the genetic disease is associated with abnormally elevated levels of an mRNA, a protein, or combination thereof.

32. The use of claim 31, wherein the composition comprises a RNA-programmable nuclease that specifically binds and cleaves a gene encoding a pathogenic RNA or protein, or a gene encoding an RNA or protein that is expressed at abnormally high levels in diseased cells or tissue, optionally wherein the medicament is to be administered under conditions sufficient for the RNA-programmable nuclease to penetrate a cell of a subject, and optionally wherein administration of the medicament comprises a route of administration selected from the group consisting of oral, intravenous, intramuscular, intra-arterial, subcutaneous, intraventricular, topical, inhalational, and mucosal delivery.

33. An ex-vivo/in-vitro method of introducing an RNA-programmable nuclease into a cell, the method comprising contacting the cell with the composition of any one of claims 1-26 or with the pharmaceutical composition of any one of claims 27-30, under conditions suitable for the functional effector protein to enter the cell, thereby introducing the functional effector protein into the cell, optionally wherein the cell is a somatic cell, and optionally wherein the cell is contacted with the composition or the pharmaceutical composition in an amount, for a time, and under conditions sufficient to induce programming of the cell to a desired cell fate.

34. The method of claim 33, further comprising confirming that the RNA-programmable nuclease has penetrated the cell, optionally wherein the programmed cell is to be used in a cell replacement therapeutic approach, and optionally wherein the cell is contacted *ex vivo* and is to be re-administered to the subject after successful targeting of the undesired allele by the nuclease.

35. The method of claim 33 or 34, wherein the cell is obtained from a subject diagnosed with having or being at risk of developing a disorder associated with an abnormal expression level of a gene, and wherein the RNA-programmable nuclease modulates the expression level of the gene, optionally wherein the cell is a cell carrying a genomic allele associated with a disease and the functional effector protein is a nuclease specifically targeting the allele.

36. A kit comprising the composition of any one of claims 1-26 or the pharmaceutical composition of any one of claims 27-30.

37. A kit for carrying out the method of any one of claims 33-35, wherein the kit comprises the composition of any one of claims 1-26, or the pharmaceutical composition of any one of claims 27-30.

38. **The composition of any one of claims 1-26 or the pharmaceutical composition of any one of claims 27-30 for use in medicine.**