

CLAIMS:

1. A nanoparticulate composition comprising a gene editing ribonucleoprotein system complexed within a poly-beta amino ester hyperbranched polymer.
- 5 2. A nanoparticulate composition according to Claim 1, in which the hyperbranched polymer is a 3-branching poly-beta amino ester hyperbranched polymer or a 4-branching poly-beta amino ester hyperbranched polymer.
- 10 3. A nanoparticulate composition according to Claim 1, in which the hyperbranched polymer is a 4-branching poly-beta amino ester hyperbranched polymer.
4. A nanoparticulate composition according to any preceding Claim, in which the gene editing ribonucleoprotein system is a CRISPR-Cas gene editing system configured to excise a mutation or exon in a gene, replace a mutation in a gene, or produce a knock-down or knock-out of a gene.
- 15 5. A nanoparticulate composition according to Claim 4, in which the gene editing ribonucleoprotein system is a CRISPR-Cas9 gene editing system configured to excise exon 80 of the COL7A1 gene which codes for the collagen VII protein.
- 20 6. A nanoparticulate composition according to any preceding Claim having an average dimension of 100 nm to 300 nm.
- 25 7. A conjugate comprising a nanoparticulate composition according to any preceding Claim, and (a) a targeting ligand configured to target the nanoparticulate composition to a specific target cell or tissue type or (b) an imaging label.
8. A pharmaceutical composition comprising a nanoparticulate composition according to any of Claims 1 to 6 or a conjugate of Claim 7 in combination with a suitable pharmaceutical excipient.
- 30 9. A pharmaceutical composition according to Claim 8 formulated for topical application to the skin or sub-dermal injection into the skin.

10. A method of making a nanoparticulate composition comprising the steps of:
- providing a solution of gene editing ribonucleoprotein system in a buffer;
 - providing a solution of cationic polymer in a suitable non-aqueous solvent;
 - 5 mixing the solutions such that there is an excess of mass of the cationic polymer over that of the gene editing ribonucleoprotein system in the mixture; and
 - resting the mixture to allow the nanoparticulate composition to form.
11. A method according to Claim 10, in which the cationic polymer is a poly-beta amino ester hyperbranched polymer.
12. A method according to Claim 11, in which the hyperbranched polymer is a 3-branching poly-beta amino ester hyperbranched polymer or a 4-branching poly-beta amino ester hyperbranched polymer.
13. A method according to any of Claims 10 to 12, in which the cationic polymer solution is prepared by dissolving the cationic polymer in DMSO, and then dilution of the solution in an aqueous buffer.
14. A method according to any of Claims 10 to 13, in which the cationic polymer is dissolved in the solvent at a concentration of 10 to 200 mg/ml.
15. A method according to any of Claims 10 to 14, in which the solution of cationic polymer after dilution with the buffer comprises 0.1 to 100 g of cationic polymer.
16. A method according to any of Claims 10 to 15, in which the gene editing ribonucleoprotein system is selected from the group comprising: CRISPR-Cas gene editing system; a zinc finger nuclease systems; and a TALEN system.
17. A method according to Claim 16, in which the method comprises a step of assembly of the gene editing ribonucleoprotein system comprising mixing a sgRNA with a Cas9 nuclease at a molar ratio between 1.1-9.0 :1 to provide a gene editing ribonucleoprotein system typically containing 0,1 to 100 µg of ribonucleoprotein complex.

18. A method according to any of Claims 10 to 17, in which the ribonucleoprotein complex is diluted in a volume of a given buffer such that the final ribonucleoprotein complex solution does not exceed that of 50% of the total desired application volume.

5 19. A method according to any of Claims 10 to 18, in which the first and second solutions are mixed at a volumetric ratio of about 1-100:1-100, such that there is an excess of mass of the cationic polymer over that of the gene editing ribonucleoprotein system.

20. A method according to any of Claims 10 to 19, in which the buffer is configured to have
10 a pH in the range of 3 to 10.

21. A method according to any of Claims 10 to 20, in which the amount of cationic polymer in the second solution is 1 to 100 times more than the ribonucleoprotein complex in terms of mass, and in which the first and second solutions are mixed at a volumetric ratio of
15 about 1-100:1-100.

22. A nanoparticulate composition according to any of Claims 1 to 6, for use in a method of treatment of a genetic disease in an individual characterised by a mutation in a gene of the individual, wherein the gene editing ribonucleoprotein system is configured to edit the gene
20 to delete or replace the mutation or a section of the gene including the mutation or restore the function of the gene, and wherein the nanoparticulate composition is administered to the individual.

23. A nanoparticulate composition of Claim 22, for use of Claim 22, in which the genetic
25 disease is a skin genetic disorder.

24. A nanoparticulate composition of Claim 22, for use of Claim 23, in which the skin genetic disorder is Recessive Dystrophic subtype of Epidermolysis Bullosa (RDEB), and wherein the gene editing ribonucleoprotein system is configured for collagen VII exon 80
30 skipping.

25. A nanoparticulate composition of Claim 22, for use of Claim 23 or 24, in which the nanoparticulate composition is administered topically or sub-dermally to the skin of the individual.

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26. A nanoparticulate composition according to any of Claims 1 to 6, for use in an ex-vivo method of treatment of a genetic disease in an individual characterised by a mutation in a gene in cells of the individual, wherein the gene editing ribonucleoprotein system is configured to edit the gene to delete or replace the mutation or a section of the gene including the mutation or restore the function of the gene, wherein the method comprises removing cells from the individual comprising the mutation, treating the cells with the nanoparticulate composition to genetically modify the cells, and implanting the genetically modified cells into the individual.
27. A nanoparticulate composition according to any of Claims 1 to 6, for use in a method of treatment of an inflammatory disease in an individual characterised by over-expression of an inflammatory mediator, wherein the gene editing ribonucleoprotein system is configured to edit the genome of the individual to effect a reduction in expression of the inflammatory mediator.
28. A nanoparticulate composition according to any of Claims 1 to 6, for use as a medicament.