CLAIMS

We claim:

1. A method for delivery of messenger RNA (mRNA) to a subject for *in vivo* production of a protein or a peptide in the subject, comprising administering to the subject by rectal delivery, a composition comprising an mRNA that encodes a protein or a peptide and is encapsulated within a lipid nanoparticle and wherein the administering of the composition results in expression of the protein or the peptide encoded by the mRNA that is detectable in the subject at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

2. The method of claim 1, wherein the protein or the peptide encoded by the mRNA is detectable in the subject's circulation at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

3. The method of claim 1, wherein the protein or the peptide encoded by the mRNA is detectable in the subject's liver at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

4. The method of claim 1, wherein the protein or the peptide encoded by the mRNA is detectable in the subject's kidney at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

5. The method of claim 1, wherein the protein or the peptide encoded by the mRNA is detectable in the subject's colon at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

6. The method of claim 1, wherein the protein or the peptide encoded by the mRNA is detectable in the subject's rectum at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

7. The method of claim 1, wherein the *in vivo* production of the protein or the peptide is in the subject's circulation, liver, kidney, colon and/or rectum.

8. The method of any one of the preceding claims, wherein the lipid nanoparticle comprises one or more cationic lipids, one or more non-cationic lipids and one or more PEG-modified lipids.

9. The method of any one of the preceding claims, wherein the lipid nanoparticle comprises cholesterol.

10. The method of any one of the preceding claims, wherein the rectal delivery is by suppository, enema, catheter or a bulb syringe.

11. The method of claim 10, wherein the rectal delivery is by suppository.

12. The method of claim 11, wherein the composition does not comprise a lipid-based suppository component.

13. The method of claim 12, wherein the lipid-based suppository component is cocoa butter, theobroma oil, synthetic fats or synthetic bases.

14. The method of any one of the preceding claims, wherein the composition comprises a permeability enhancer.

15. The method of claim 14, wherein the permeability enhancer is selected from bile salts, surfactants, fatty acids and derivatives, glycerides, chelators, salicylates, or polymers.

16. The method of claim 15, wherein the fatty acids and derivatives are selected from sorbitan laurate, sodium caprate, sucrose, palitate, lauroyl choline, sodium myristate, or palmitoyl carnitine.

17. The method of claim 14, wherein the permeability enhancer is a form of caprate.

18. The method of claim 18, wherein the caprate-based permeability enhancer is sodium caprate.

19. The method of claim 14, wherein the permeability enhancer is Labrasol®.

20. The method of any one of the preceding claims, wherein the composition comprises a water-based suppository component.

21. The method of claim 20, wherein the water-based suppository component is selected from glycerin, gelatin or polyethylene glycol (PEG), or combinations thereof.

22. The method of any one of the preceding claims, wherein the composition further comprises gelatin.

23. The method of claim 22, wherein the only water-based suppository component is gelatin.

24. The method of claim 23, wherein the composition comprises about 5% or more gelatin in water, 10% or more gelatin in water, 20% or more gelatin in water, 30% or more gelatin in water, or 50% or more gelatin in water.

25. The method of any one of the preceding claims, wherein the composition further comprises 0.25 mg/mL or greater mRNA, 0.5 mg/mL or greater mRNA, 0.75 mg/mL or greater mRNA, or 1 mg/mL or greater mRNA.

26. The method of claim 25, wherein the composition comprises 0.5 mg or greater mRNA, 0.75 mg or greater mRNA, 1 mg or greater mRNA, 1.25 mg or greater mRNA, 1.5 mg or greater mRNA, or 1.75 mg or greater mRNA.

27. The method of any one of claims 11-26, wherein the composition is formulated for a suppository of about 3 grams, about 2 grams, or about 1 gram.

28. The method of claim 27, wherein the composition is formulated for a suppository of about 3 grams.

29. The method of any one of claims 11-26, wherein the composition is formulated for a suppository having a volume of about 2.0 mL, about 3.5 mL, about 7.5 mL, or about 10.0 mL.

~~30. The method of any one of claims 11-29, wherein the suppository is refrigerated prior to administration.~~

~~31. The method of any one of the preceding claims, wherein the subject is first administered a permeability enhancer prior to the administering of the composition comprising mRNA.~~

~~32. The method of claim 31, wherein the permeability enhancer is administered to the subject about 30 minutes, about 1 hour, about 2.5 hours, about 5 hours, or about 12 hours prior to administering the composition comprising mRNA.~~

~~33. The method of claim 32, wherein the permeability enhancer is administered about 30 minutes prior to administering the composition comprising mRNA.~~

~~34~~1. A ~~method of delivery of messenger RNA (mRNA) to a subject for *in vivo* production of a protein or peptide in the subject, comprising administering to the subject by mucosal delivery a~~ composition comprising a~~n~~ messenger RNA (mRNA) that encodes a protein or a peptide and is encapsulated within a lipid nanoparticle for use in the treatment of a disease in a subject in need thereof, ~~and~~ wherein ~~the administering of~~ the composition is to be administered to the subject by mucosal delivery and wherein the composition administered results in expression of the protein or peptide encoded by the mRNA that is detectable in the subject at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.

2. The composition for use according to claim 1, wherein the mucosal delivery is
   a. rectal,
   b. vaginal,
   c. ocular,
   d. oral, optionally wherein the oral delivery is buccal or sublingual, or
   e. gastrointestinal;

   optionally wherein the mucosal delivery is the rectal delivery.

~~35. The method of claim .34, wherein the mRNA is detectable in the subject's circulation, liver, kidney, colon, and/or rectum at least about 24 hours, about 48 hours, about 72 hours, or about 96 hours after administration.~~

~~36. The method of claim 34 or 35, wherein the mucosal delivery is rectal, vaginal, ocular, oral, or gastrointestinal.~~

~~37. The method of claim 36, wherein the oral delivery is buccal or sublingual.~~

~~38. The method of any one of claims 33-37, wherein the mucosal delivery is rectal.~~

3~~9~~. The ~~method of any one of claims 33-37~~composition for use according to claim 1 or 2, wherein ~~the *in vivo* production of~~ the protein or peptide is expressed in the subject's circulation, liver, kidney, colon and/or rectum.

4. The composition for use according to any one of claims 1-3, wherein the lipid nanoparticle comprises:
    a. one or more cationic lipids, one or more non-cationic lipids and one or more PEG- modified lipids and/ or
    b. cholesterol.

5. The composition for use according to any one of claims 1-4, wherein the rectal delivery is by suppository, enema, catheter or a bulb syringe.

6. The composition for use according to claim 5, wherein the rectal delivery is by suppository, wherein the composition does not comprise a lipid-based suppository component, optionally wherein the lipid-based suppository component is cocoa butter, theobroma oil, synthetic fats or synthetic bases.

7. The composition for use according to any one of claims 1-6, wherein the composition comprises a permeability enhancer, optionally wherein the permeability enhancer
    a. is selected from:
        i. bile salts,
        ii. surfactants,

iii. fatty acids and derivatives, optionally selected from sorbitan laurate, sodium caprate, sucrose, palitate, lauroyl choline, sodium myristate, or palmitoyl carnitine,

iv. glycerides,

v. chelators,

vi. salicylates, or

vii. polymers; or

b. is a form of caprate, optionally wherein the caprate-based permeability enhancer is sodium caprate; or

c. is Labrasol®.

8. The composition for use according to any one of claims 1-7, wherein the composition comprises a water-based suppository component, optionally wherein the water-based suppository component is selected from glycerin, gelatin or polyethylene glycol (PEG), or combinations thereof, optionally wherein the only water-based suppository component is gelatin, optionally wherein the composition comprises about 5% or more gelatin in water, 10% or more gelatin in water, 20% or more gelatin in water, 30% or more gelatin in water, or 50% or more gelatin in water.

9. The composition for use according to any one of claims 1-8, wherein the composition comprises 0.25 mg/mL or greater mRNA, 0.5 mg/mL or greater mRNA, 0.75 mg/mL or greater mRNA, or 1 mg/mL or greater mRNA;
optionally wherein the composition comprises 0.5 mg or greater mRNA, 0.75 mg or greater mRNA, 1 mg or greater mRNA, 1.25 mg or greater mRNA, 1.5 mg or greater mRNA, or 1.75 mg or greater mRNA.

10. The composition for use according to any one of claims 1-9, wherein the composition is formulated for a suppository of about 3 grams, about 2 grams, or about 1 gram, and/or having a volume of about 2.0 mL, about 3.5 mL, about 7.5 mL, or about 10.0 mL.

11. The composition for use according to any one of claims 1-10, wherein the suppository is refrigerated prior to administration.

12. The composition for use according to any one of claims 1-11, wherein the subject is first to be administered a permeability enhancer prior to the administration of the composition comprising mRNA, optionally wherein the permeability enhancer is to be administered to the subject about 30 minutes, about 1 hour, about 2.5 hours, about 5 hours, or about 12 hours prior to the administration of the composition comprising mRNA, optionally wherein the permeability enhancer is to be administered about 30 minutes prior to the administration of the composition comprising mRNA.

~~40~~13. A suppository for rectal administration of mRNA, the suppository comprising:

a. mRNA encapsulated within a lipid nanoparticle, wherein the mRNA encodes a protein or peptide~~.~~; and

b. gelatin.

~~41~~14. The suppository of claim ~~40~~13, comprising about 5% or more gelatin in water, 10% or more gelatin in water, 20% or more gelatin in water, 30% or more gelatin in water, or 50% or more gelatin in water.

~~42~~15. The suppository of ~~any one of~~ claim ~~40~~13 or ~~41~~14, wherein the suppository does not comprise a lipid-based suppository component, optionally wherein the lipid-based suppository component is cocoa butter, theobroma oil, synthetic fats or synthetic bases.

16. The suppository of any one of claims 13-15, further comprising a permeability enhancer, glycerin and/or PEG, optionally wherein the permeability enhancer

a. is selected from

i. bile salts,

ii. surfactants,

iii. fatty acids and derivatives, optionally wherein the fatty acids and derivatives are selected from sorbitan laurate, sodium caprate, sucrose, palitate, lauroyl choline, sodium myristate, or palmitoyl carnitine,

iv. glycerides,

v. chelators,

vi. salicylates, or

vii. polymers; or

b. is a form of caprate, optionally wherein the caprate-based permeability enhancer is sodium caprate; or

c. is Labrasol®.

~~43. The suppository of claim 42, wherein the lipid-based suppository component is cocoa butter, theobroma oil, synthetic fats or synthetic bases.~~

~~44. The suppository of any one of claim 40-43, further comprising a permeability enhancer.~~

~~45. The suppository of claim 44, wherein the permeability enhancer is selected from bile salts, surfactants, fatty acids and derivatives, glycerides, chelators, salicylates, or polymers.~~

~~46. The suppository of any one of claims 40-45, wherein the fatty acids and derivatives are selected from sorbitan laurate, sodium caprate, sucrose, palitate, lauroyl choline, sodium myristate, or palmitoyl carnitine.~~

~~47. The suppository of any one of claims 40-45, wherein the permeability enhancer is a form of caprate.~~

~~48. The suppository of claim 47, wherein the caprate-based permeability enhancer is sodium caprate.~~

~~49. The suppository of 44, wherein the permeability enhancer is Labrasol®.~~

~~50. The suppository of any one of claims 40-49, further comprising glycerin and/or PEG.~~

~~51~~17. The suppository of any one of claims ~~40-50~~13-16, wherein the suppository softens or melts at about between 36 and 37°C.