CLAIMS

We claim:

1. A composition comprising a 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, wherein:
   the composition is to be administered to the subject by rectal delivery;
   the administration of the composition results in expression of the protein or peptide encoded by the mRNA that is detectable in the subject at least 24 hours to 96 hours after administration;
   the subject is first to be administered a permeability enhancer by rectal delivery prior to the administration of the composition by rectal delivery; and
   the permeability enhancer comprises Labrasol® (PEG-8 caprylic/capric glycerides), a form of caprate, sorbitan laurate, palmitate, lauroyl choline, sodium myristate, or palmitoyl carnitine.

2. The composition for use according to claim 1, wherein the protein or peptide is expressed in the subject's circulation, liver, kidney, colon and/or rectum.

3. The composition for use according to claim 1 or 2, wherein the lipid nanoparticle comprises one or more cationic lipids, one or more non-cationic lipids and one or more PEG-modified lipids.

4. The composition for use according to claim 3, wherein the lipid nanoparticle further comprises cholesterol.

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

6. The composition for use according to claim 5, wherein the composition is a suppository.

7. The composition for use according to any one of claims 1-6, wherein the permeability enhancer is sodium caprate or Labrasol® (PEG-8 caprylic/capric glycerides).

8. The composition for use according to any one of claims 1-7, wherein the composition comprises a water-based suppository component selected from glycerin, gelatin or polyethylene glycol (PEG), or combinations thereof.

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

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

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

12. The composition for use according to any one of claims 1-11, wherein the permeability enhancer is to be administered to the subject from 30 minutes to 12 hours prior to the administration of the composition, optionally wherein the permeability enhancer is to be administered from 30 minutes to 1 hour prior to the administration of the composition.

13. The composition for use according to any one of claims 1-12, wherein the composition is a suppository comprising gelatin.

14. The composition for use according to claim 13, wherein the suppository comprises 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.

15. The composition for use according to claim 13 or 14, wherein the suppository does not comprise cocoa butter, theobroma oil, or a synthetic fat.

16. The composition for use according to any one of claims 13-15, wherein the suppository softens or melts at between 36°C and 37°C.