

CLAIMS

1. Use of a cytosolic DNA-sensing inhibitor selected from the group consisting of a cyclic GMP-AMP synthase - stimulator of interferon genes (cGAS - STING) pathway inhibitor and an inflammasome pathway inhibitor in the manufacture of a medicament for use in a method of intracellular delivery of a DNA to a subject, wherein:
 - a. at least one of the cytosolic DNA-sensing inhibitor is to be administered to the subject; and
 - b. a first nanoparticle comprising said DNA is to be administered prior to, concomitantly with, or after (a).
2. The use of claim 1, wherein if said first nanoparticle is a lipid nanoparticle then at least one of (i) said cytosolic DNA-sensing inhibitor is at least said inflammasome pathway inhibitor; (ii) said lipid nanoparticle does not comprise an endosomolytic agent; (iii) said DNA is circular; (iv) said DNA is not closed-ended DNA; or (v) said cytosolic DNA-sensing inhibitor is provided in a second nanoparticle, wherein said second nanoparticle has the same or different composition as said first nanoparticle.
3. The use of claims 1 or 2, wherein said DNA is a DNA vector comprising a transgene operatively linked to a regulatory element.
4. The use of claim 3, wherein said transgene is operatively linked to a promoter; and said DNA vector comprises 5' to 3' said promoter, said transgene, and a polyadenylation and termination signal.
5. The use of claim 4, wherein said promoter is a promoter/enhancer and said vector further comprises a regulatable element.
6. The use of claim 4, wherein said inhibitor is a STING inhibitor.
7. The use of any one of claims 1-5, wherein said cytosolic DNA-sensing inhibitor is a cGAS-STING pathway inhibitor.
8. The use of claim 7, wherein said cGAS-STING pathway inhibitor is

- i) a cGAS inhibitor;
- ii) a STING inhibitor;
- iii) a TBK1 inhibitor; or
- iv) (a) selected from the group consisting of H-151, GSK-690693, RU-521, RO-3150, CYT387 and GSK8612, or a pharmaceutically acceptable salt thereof; or (b) is a compound of Table 1, Table 2, or Table 3, or a pharmaceutically acceptable salt thereof.

9. The use of any one of claims 1 to 5, wherein said cytosolic DNA-sensing inhibitor is an inflammasome pathway inhibitor.

10. The use of claim 9, wherein said inflammasome pathway inhibitor is an AIM2 inhibitor, optionally wherein said inflammasome pathway inhibitor is a polynucleotide having the sequence of SEQ ID NO: 1 or SEQ ID NO: 2.

11. The use of any one of claims 3-10, wherein said transgene encodes a viral antigen, a bacterial antigen, a therapeutic protein, a short hair pin RNA (shRNA), a small interfering RNA (siRNA), a microRNA (miRNA), an RNAi, a ribozyme, an antisense RNA, a clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 construct, a zinc finger nuclease (ZFN), or a transcription activator-like effector nuclease (TALEN).

12. The use of any one of claims 1-11, wherein said DNA is circular DNA.

13. The use of any one of claims 1-12, wherein said cytosolic DNA-sensing inhibitor is provided in a second nanoparticle, wherein said second nanoparticle has substantially the same composition as said first nanoparticle or, where said DNA vector and said cytosolic DNA-sensing inhibitor are provided together in said first nanoparticle.

14. The use of any one of claims 1-13, wherein said first nanoparticle is a lipid nanoparticle or a lipid polymer nanoparticle.

15. The use of claim 14, wherein said first nanoparticle is configured to release said cytosolic DNA-sensing inhibitor prior to the release of said DNA or said DNA vector.

16. The use of any one of claims 1-14, wherein said cytosolic DNA-sensing inhibitor is to be administered at about the same time up to about 4 hours prior to administration of said DNA or said DNA vector.
17. The use of any one of claims 1-16, wherein both an inflammasome inhibitor and a cGAS – STING inhibitor are to be administered.
18. The use of any one of claims 1-17, wherein said DNA substantially comprises double-stranded DNA and said DNA vector substantially comprises double-stranded DNA.
19. The use of any one of claims 3-18, wherein said subject is a human patient, and a therapeutically effective amount of said transgene is provided by the use.
20. A nanoparticle composition comprising
- c. a DNA; and
 - d. at least one cytosolic DNA-sensing inhibitor selected from the group consisting of a cyclic GMP-AMP synthase (cGAS) – STING pathway inhibitor and an inflammasome pathway inhibitor.
21. The composition of claim 20, wherein said DNA is a DNA vector comprising a transgene operatively linked to a regulatory element.
22. The composition of claim 21, wherein said DNA vector comprises 5' to 3' a promoter, said transgene, and a polyadenylation and termination signal.
23. The composition of claim 22, wherein said promoter is a promoter/enhancer and said vector further comprises a regulatable element.
24. The composition of any one of claims 20 to 23, wherein said inhibitor is a cGAS-STING pathway inhibitor.
25. The composition of claim 24, wherein said cGAS-STING pathway inhibitor is
- i) a cGAS inhibitor;
 - ii) a STING inhibitor;

- iii) a TBK1 inhibitor; or
- iv) (a) selected from the group consisting of H-151, GSK-690693, RU-521, RO-3150, CYT387 and GSK8612, or a pharmaceutically acceptable salt thereof; or (b) is a compound of Table 1, Table 2, or Table 3, or a pharmaceutically acceptable salt thereof.
26. The composition of any one of claims 20 to 23, wherein said cytosolic DNA-sensing inhibitor is an inflammasome pathway inhibitor.
27. The composition of claim 26, wherein said inflammasome pathway inhibitor is an AIM2 inhibitor, optionally wherein said inflammasome pathway inhibitor is a polynucleotide having the sequence of SEQ ID NO: 1 or SEQ ID NO: 2.
28. The composition of any one of claims 20 to 27, wherein said transgene encodes a viral antigen, a bacterial antigen, a therapeutic protein, a short hair pin RNA (shRNA), a small interfering RNA (siRNA), a microRNA (miRNA), a RNA_i, a ribozyme, an antisense RNA, a clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 construct, a zinc finger nuclease (ZFN), or a transcription activator-like effector nuclease (TALEN).
29. The composition of any one of claims 20 to 28, wherein said DNA vector is circular DNA.
30. The composition of any one of claims 20 to 29, wherein said nanoparticle is a lipid nanoparticle or a lipid polymer nanoparticle.
31. The composition of claim 30, wherein said nanoparticle is a lipid polymer nanoparticle configured to release said cytosolic DNA-sensing inhibitor prior to said DNA vector.
32. The composition of any one of claims 20 to 31, wherein said nanoparticle comprises both an inflammasome inhibitor and a cGAS – STING inhibitor.
33. The composition of any one of claims 20 to 32, wherein said DNA substantially comprises double-stranded DNA and said DNA vector substantially comprises double-stranded DNA.
34. A pharmaceutical composition comprising the nanoparticle composition of any one of claims 20-33 and a pharmaceutically acceptable carrier.
35. The pharmaceutical composition of claim 34 for use in medicine.