Development of STAT3 inhibitors has been hampered by the lack of a tyrosine kinase domain on STAT3, as well as the close homology of STAT3 to other members of the STAT signaling pathway. Thus, there remains an unmet need for therapeutic compositions and methods targeting expression of STAT3, and disease processes associated therewith.

SUMMARY ~~OF THE INVENTION~~

[0005] In one ~~aspect~~example, there is provided a nucleic acid comprising an oligonucleotide strand of 15-80 nucleotides in length, wherein said oligonucleotide strand is at least 80% complementary to a target STAT3 mRNA sequence along at least 15 nucleotides of said oligonucleotide strand, wherein the target STAT3 mRNA sequence has the sequence of AGGUCAAACCCUUAAGACAUCUGAAGCUGCAACCUGGCCUUUGGUGUUGAAAUAGGA AGGUUUAAGGAGAAUCUAAGCAUU (SEQ ID NO: 1).

[0005a] In one aspect, the present disclosure refers to a nucleic acid for inhibiting expression of STAT3, comprising an oligonucleotide strand of 15-80 nucleotides in length, wherein said oligonucleotide strand is at least 80% complementary to a target STAT3 mRNA sequence along at least 15 nucleotides of said oligonucleotide strand, wherein the target STAT3 mRNA sequence has the sequence of SEQ ID NO: 1.

[0006] In another aspect the present disclosure refers to ~~, there is provided~~ a double stranded nucleic acid (dsNA) for inhibiting expression of *STAT3*, comprising a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand is at least 80% complementary to a target STAT3 mRNA sequence along at least 15 nucleotides of said antisense strand, wherein the target STAT3 mRNA sequence has the sequence of SEQ ID NO: 1; and wherein the sense strand is at least 80% complementary to the sequence AAUGCUUAGAUUCUCCUUAAACCUUCCUAUUUCAACACCAAAGGCCAGGUUGCAGCUU CAGAUGUCUUAAGGGUUUGACCUGA (SEQ ID NO: 2), along at least 15 nucleotides of said sense strand.

[0007] In ~~one~~ yet another aspect the present disclosure refers to~~, there is provided~~ an agent for inhibiting expression of *STAT3*, comprising an aptamer and a double strand nucleic acid (dsNA), said dsNA comprising a sense strand and an antisense strand; wherein the aptamer is attached to one end of the antisense strand via a linker; wherein the aptamer comprises a sequence which differs by no more than 3 nucleotides from SEQ ID NO: 15; and wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NO: 10 SEQ ID NOs: 12, and SEQ ID NOs: 14.

[0008] In ~~one~~ still another aspect the present disclosure refers to~~, there is provided~~ a nanoparticle comprising the nucleic acid, the dsNA, and/or the agent as disclosed herein.

[0009] In one ~~aspect~~example, there is provided a method of treating cancer in a subject, comprising administering an effective amount of the nucleic acid, the dsNA, the agent, and/or the nanoparticle as disclosed herein.

[0010] In still another aspect the present disclosure refers to~~, there is provided~~ the nucleic acid, the dsNA, the agent, and/or the nanoparticle as disclosed herein for use in therapy.

[0011] In still another aspect the present disclosure refers to~~, there is provided~~ use of the nucleic acid, the dsNA, the agent, and/or the nanoparticle as disclosed herein in the manufacture of a medicament for treating cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0013] **Figure 1** is a diagram depicting the region targeted by commercially available STAT3 siRNAs. Five functionally validated sequences (Dh1, Dh3, Dh4, Q7 and Q8) were purchased from two companies (Dh and Q). As shown in the diagram, all five commercially available siRNAs target the coding region of *STAT3*.

[0014] **Figure 2** shows the results of RT-qPCR quantification of the mRNA level of *STAT1*, *STAT2*, *STAT3*, *STAT4*, *STAT5A* and *STAT5B* in H2170 cancer cell lines transfected with the different commercially available STAT3 siRNAs (Dh1, Dh3, Dh4, Q7 and Q8). 50nM of each siRNA was used, and JetPrime Transfection reagent was used according to manufacturer's protocol. Total RNA was harvested 48 hours post-transfection. GAPDH was used as endogenous control. The results show that each of the five commercially available STAT3 siRNA sequences exhibit non-specific inhibition of other STAT isoforms in H2170 cell line.

[0015] **Figure 3** is a diagram depicting the region targeted by the STAT3 DsiRNAs (Si-1, Si-2 and Si-3) as encompassed by the present invention. As shown in the diagram, the sequences targeted by all three STAT3 DsiRNAs lie within a short 81-nt target region in the 3'UTR region of *STAT3*.

[0016] **Figure 4** shows the results of RT-qPCR quantification of the mRNA level of *STAT1*, *STAT2*, *STAT3*, *STAT4*, *STAT5A* and *STAT5B* in two lung cancer cell lines, H2170 and PC9. 50nM of each customized STAT3 DsiRNAs was used, and JetPrime Transfection

Claims:

1. A nucleic acid for inhibiting expression of STAT3, comprising an oligonucleotide strand of 15-80 nucleotides in length, wherein said oligonucleotide strand is at least 80% complementary to a target STAT3 mRNA sequence along at least 15 nucleotides of said oligonucleotide strand, wherein the target STAT3 mRNA sequence has the sequence of SEQ ID NO: 1.

2. A double stranded nucleic acid (dsNA) for inhibiting expression of STAT3, comprising a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand is at least 80% complementary to a target STAT3 mRNA sequence along at least 15 nucleotides of said antisense strand, wherein the target STAT3 mRNA sequence has the sequence of SEQ ID NO: 1; and wherein the sense strand is at least 80% complementary to a sequence provided in SEQ ID NO: 2, along at least 15 nucleotides of said sense strand.

3. The dsNA of claim 2, wherein the sense strand comprises at least 15 contiguous nucleotides that are at least 80% complementary to a nucleotide sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NOs: 6, and SEQ ID NOs: 8; and wherein the antisense strand comprises at least 15 contiguous nucleotides that are at least 80% complementary to a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NOs: 5, and SEQ ID NOs: 7.

4. The dsNA of any of claim 2 or 3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NOs: 11, and SEQ ID NOs: 13; and wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NO: 10 SEQ ID NOs: 12, and SEQ ID NOs: 14.

5. The dsNA of any of claims 2-4, wherein the sense strand is 15-80 nucleotides in length and the antisense strand is 19-80 nucleotides in length.

6. The dsNA of any of claims 2-5, wherein the sense strand is 15-35 nucleotides in length and the antisense strand is 19-35 nucleotides in length.

7. The dsNA of any of claims 2-6, wherein the dsNA comprises a duplex region selected from the group consisting of 19, 20, 21, 22, 23, 24, 25, 26, or 27 base pairs.

8. The dsNA of any of the claims 2-7, wherein the antisense strand comprises 1-5 single-stranded nucleotides at its 3' terminus, optionally 1-3 nucleotides in length, and optionally 2 nucleotides in length.

9. The nucleic acid of claim 1 or the dsNA of any of claims 2-8, comprising at least one modified nucleotide, wherein the at least one modified nucleotide is modified at the 2' position, the 3' position, the 5' position or the 6' position.

10. The nucleic acid or the dsNA of claim 9, wherein the at least one modified nucleotide is selected from the group consisting of a deoxy-nucleotide, a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, a nucleotide comprising a 5'-phosphate mimic, a glycol modified nucleotide (GNA), and a 2-O-(N-methylacetamide) modified nucleotide; and combinations thereof.

11. The nucleic acid of claim 1, 9, 10 or the dsNA of any of claims 2-10, comprising a phosphate backbone modification selected from the group consisting of a phosphorothioate, a chiral phosphorothioate, a phosphorodithioate, a phosphotriester, an aminoalkylphosphotriester, a methyl or other alkyl phosphonate, a phosphinate, a phosphoramidate including 3'-amino phosphoramidate and aminoalkylphosphoramidate, a thionophosphoramidate, a thionoalkylphosphonate, a thionoalkylphosphotriester, and a boranophosphate.

12. The nucleic acid of claim 1, 9-11, or the dsNA of any of claims 2-11, wherein the oligonucleotide strand, or at least one strand of the dsNA is attached to at least one moiety, optionally wherein the addition of the at least one moiety provides the nucleic acid or the dsNA with one or more of the following characteristics: increased stability/increased half-life, increased bioavailability, reduced renal clearance, reduced *in vivo* toxicity, increased cellular uptake, and increased affinity to a specific cell type or a specific molecule.

13. The nucleic acid or the dsNA of claim 12, wherein the at least one moiety is selected from the group consisting of a polyethylene glycol (PEG), a cholesterol, a dialkyl lipid, a protein, an organic or inorganic nanomaterial, and an inert antibody, and wherein the at least one moiety is at the 5’ end of the oligonucleotide strand or the antisense strand.

14. The nucleic acid of claim 1, 9-13, or the dsNA of any of claims 2-13, wherein the nucleic acid or the dsNA is formulated with poloxamer gel or a molecule to increase the molecular mass of the nucleic acid or the dsNA to more than about 30-50 kDa.

15. The nucleic acid or the dsNA of claim 12, wherein the at least one moiety comprises an aptamer.

16. The nucleic acid or the dsNA of claim 15, wherein the aptamer is an anti-transferrin receptor (anti-TfR) aptamer, optionally an anti-human transferrin receptor (anti-hTfR) aptamer.

17. The nucleic acid or the dsNA of claim 15 or 16, wherein the aptamer comprises a sequence which differs by no more than 3 nucleotides from SEQ ID NO: 15.

18. The nucleic acid or the dsNA of any of claims 12-17, wherein the moiety is attached to the oligonucleotide strand or the antisense strand via a linker.

19. The nucleic acid or the dsNA of claim 18, wherein the linker comprises a hydrocarbon linker, wherein the hydrocarbon linker is optionally a C3 carbon linker.

20. The nucleic acid or the dsNA of claim 18 or 19, wherein the linker comprises a polynucleotide linker.

21. The nucleic acid or the dsNA of claim 20, wherein the polynucleotide linker comprises the sequence of SEQ ID NO: 16.

22. The nucleic acid or the dsNA of claim 18, wherein the linker comprises a hydrocarbon linker and a polynucleotide linker, resulting in a molecule comprising the structure of: [moiety]-[hydrocarbon linker]-[polynucleotide linker]-[oligonucleotide strand/antisense strand of the nucleic acid/dsNA], wherein each "]-[" represents a covalent bond.

23. The nucleic acid or the dsNA of claim 22, wherein the molecule comprises the structure of: [Aptamer]-[hydrocarbon linker]-[polynucleotide linker]-[oligonucleotide strand/antisense strand of the nucleic acid/dsNA].

24. An agent for inhibiting expression of STAT3, comprising an aptamer and a double strand nucleic acid (dsNA), said dsNA comprising a sense strand and an antisense strand; wherein the aptamer is attached to one end of the antisense strand via a linker; wherein the aptamer comprises a sequence which differs by no more than 3 nucleotides from SEQ ID NO: 15; and wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from a nucleotide

sequence selected from the group consisting of SEQ ID NO: 10 SEQ ID NOs: 12, and SEQ ID NOs: 14.

25. The agent of claim 24, wherein the dsNA comprises at least one modified nucleotide.

26. The agent of claim 22 or 23, wherein the dsNA comprises a phosphate backbone modification.

27. The agent of any one of claims 24-26, wherein at least one strand of the dsNA is attached to at least one further moiety other than the aptamer, wherein the further moiety is optionally selected from the group consisting of: a polyethylene glycol (PEG), a cholesterol, a dialkyl lipid, a protein, an organic or inorganic nanomaterial, and an inert antibody, and wherein the at least one further moiety is at the 5' end of the oligonucleotide strand or the antisense strand.

28. The agent of any one of claims 24-27, wherein the linker comprises a hydrocarbon linker and/or a polynucleotide linker.

29. A nanoparticle comprising the nucleic acid of any one of claims 1, and 3-23, the dsNA of any one of claims 2-23, and/or the agent of any one of claims 24-28.

30. The nanoparticle of claim 29, wherein the nanoparticle is a lipid nanoparticle, a polymer nanoparticle, an inorganic nanoparticle, an exosome, or a nucleic acid nanostructure.

31. The nanoparticle of claim 30, wherein the exosome is a red blood cell derived exosome.

~~32. A method of treating cancer in a subject, said method comprising administering an effective amount of the nucleic acid of any one of claims 1, 3-23, the dsNA of any one of claims 2-23, the agent of any one of claims 24-28, and/or the nanoparticle of any one of claims 29-31.~~

~~33.~~32. The nucleic acid of any one of claims 1, 3-23, the dsNA of any one of claims 2-23, the agent of any one of claims 24-28, and/or the nanoparticle of any one of claims 29-31 for use in therapy.

~~34.~~33. Use of the nucleic acid of any one of claims 1, 3-23, the dsNA of any one of claims 2-23, the agent of any one of claims 24-28, and/or the nanoparticle of any one of claims 29-31 in the manufacture of a medicament for treating cancer.

~~35.~~34. The ~~method of claim 32, or the~~ use of claim ~~34~~33, wherein the cancer is selected from the group consisting of: a lung cancer, a head and neck squamous cell carcinoma, an endemic nasopharyngeal carcinoma, a melanoma, a breast carcinoma, a prostate cancer, a renal cell carcinoma, a pancreatic carcinoma, ovarian cancer, a leukemia, a lymphoma and a hepatocellular carcinoma (HCC).

~~36.~~35. The ~~method of claim 32, or the~~ use of claim 34, wherein the lung cancer is a non-small cell lung cancer.

~~37.~~36. The ~~method or the~~ use of claim 34, wherein the leukemia is selected from the group consisting of a T-Cell Leukemia, a Large granular lymphocytic (LGL) leukemia, an Acute myeloid leukemia (AML), and a Chronic myeloid leukemia (CML).

~~38.~~37. The ~~method or the~~ use of claim 34, wherein the lymphoma is selected from the group consisting of an anaplastic large cell lymphoma, and a Burkitt's lymphoma.