supplementation are shown in (A) and patients receiving supplementation while undergoing ON treatment as shown in (B).

DETAILED DESCRIPTION

[0084] It is provided herein a demonstration that ONs chelate diverse divalent metal cations including calcium, magnesium, cobalt, iron, manganese, barium, nickel, copper, zinc, cadmium, mercury and lead. It is further demonstrated that chelation of these divalent cations results in the formation of ON chelate complexes comprised of two or more ONs linked via metal cations and occur as exemplified, but not limited to, ONs between 6 and 80 nucleotides in length, and in the presence of phosphodiester or phosphorothioate oligonucleotides. Chelation also occurs with oligonucleotides containing 2' modifications at the ribose or not. Moreover, the chelation of the metal cations is not dependent on the sequence of nucleotides present but instead relies on the physiochemical features common to all oligonucleotides (see Fig. 14A).

[0085] Herein is presented the discovery that oligonucleotides in aqueous solutions containing any simple metal cation that is divalent (such as for example but not limited to, Ca^{2+}, Mg^{2+}, Fe^{2+}) do not exist as salts but rather as chelated complexes of ONs. These complexes are comprised of oligonucleotide dimers or higher order molecular organizations in which ONs are linked at their phosphodiester backbones via divalent metal ion bridges (see Fig. 14B). At specific ON and metal cation concentrations, these chelated complexes are stable and soluble in aqueous solution and effectively sequester any divalent cations in the ON chelate complexes from solution interaction. This chelate complex formation is also likely to occur with simple metal cations with a 3+ charge or greater (as depicted in Fig. 14B). Thus ONs function as divalent cation chelaters and do not form salts with divalent cations.

[0086] Importantly, the formation of oligonucleotide chelate complexes does not occur with monovalent cations such as Na^+, K^+ or NH_4^+ and is thus unlikely to ~~not~~ occur with any monovalent cation. Thus, the term "oligonucleotide salt" is specifically limited only to oligonucleotide salts with monovalent cations or with cations which do <u>not</u> form chelate complexes with oligonucleotides and is incorrectly used to describe oligonucleotides existing in solution or in powder form with divalent metal cations (or even trivalent metal cations).

WHAT IS CLAIMED IS:

1. An oligonucleotide chelate complex comprising two or more oligonucleotides linked by a multivalent cation wherein at least one oligonucleotide of said complex has at least one phosphorothioate linkage.

2. The oligonucleotide chelate complex of claim 1, wherein said multivalent cation is a divalent metal cation.

3. The oligonucleotide chelate complex of claim 2, wherein said multivalent cation is an alkali earth metal with a 2+ charge state.

4. The oligonucleotide chelate complex of claim 2, wherein said divalent metal cation is a transition metal with a 2+ charge state.

5. The oligonucleotide chelate complex of claim 2, wherein said divalent metal cation is a lanthanide metal with a 2+ charge state.

6. The oligonucleotide chelate complex of claim 2, wherein said divalent metal cation is a post-transition metal with a 2+ charge state.

7. The oligonucleotide chelate complex of claim 2, wherein said divalent metal cation is calcium, magnesium, cobalt, iron (2+), manganese, copper or zinc.

8. The oligonucleotide chelate complex of any one of claims 1-7, wherein said chelate complex comprises two or more different divalent metal cations.

9. The oligonucleotide chelate complex of any one of claims 1-8, wherein said chelate complex comprises at least one double stranded oligonucleotide.

10. The oligonucleotide chelate complex of any one of claims 1-9, wherein said chelate complex comprises at least one fully phosphorothioated oligonucleotide.

11. The oligonucleotide chelate complex of any one of claims 1-10, wherein said chelate complex comprises at least one oligonucleotide with one 2' modified ribose.

12. The oligonucleotide chelate complex of any one of claims 1-11, wherein said chelate complex comprises at least one oligonucleotide which has each ribose 2' O-methylated.

13. The oligonucleotide chelate complex of any one of claims 1-12 adapted for subcutaneous administration.

14. The oligonucleotide chelate complex of any one of claims 1-12, adapted for at least one of the following routes of administration: intraocular, oral ingestion, enteric, inhalation, cutaneous injection, intramuscular injection, intraperitoneal injection, intrathecal injection, intrathecal infusion, intratracheal, intravenous injection, intravenous infusion, intracranial injection, intracranial infusion and topically.

15. The oligonucleotide chelate complex of claim 14, wherein said inhalation administration is an aerosol.

16. The oligonucleotide chelate complex of any one of claims 1-15, wherein said chelate complex comprises oligonucleotide selected from the group consisting of SEQ ID NOs: 3 to 14.

17. The oligonucleotide chelate complex of any one of claims 1-15, wherein said chelate complex comprises oligonucleotides selected from the group consisting of SEQ ID NOs: 3 to 14 and wherein said oligonucleotides are fully phosphorothioated.

18. An oligonucleotide formulation for subcutaneous administration, said oligonucleotide formulation comprising the oligonucleotide chelate complex of any one of claims 1-17.

19. The formulation of claim 18 further adapted for subcutaneous administration.

20. The formulation of claim 18, wherein said formulation is further adapted for at least one of the following routes of administration: intraocular, oral ingestion, enteric, inhalation, cutaneous injection, subcutaneous injection, intramuscular injection, intracranial injection, intracranial infusion, intraperitoneal injection, intrathecal injection, intrathecal infusion, intratracheal, intravenous injection, intravenous infusion, and topically.

21. The oligonucleotide formulation of claim 20, wherein said inhalation administration is an aerosol.

22. A pharmaceutical composition comprising the oligonucleotide chelate complex of any one of claims 1-17 or the oligonucleotides formulation of any one of claims 18-21 and a carrier.

23. A method for the preparation of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, the method comprising dissolving any oligonucleotide sodium salt in a pharmaceutically acceptable aqueous excipient, and gradually adding a divalent metal salt solution to the dissolved oligonucleotide such that the oligonucleotide chelate complex remains soluble.

24. The method of claim 23, wherein the dissolved oligonucleotide concentration is 0.01 – 100mg/ml prior to the metal salt addition.

25. The method of claim 23, wherein the ratio of metal salt added to the dissolved oligonucleotide is 0.1-40mg of divalent salt per 100mg of oligonucleotide.

26. The method of claim 23, wherein the final oligonucleotide concentration is 0.1-100mg/ml.

27. The method of claim 23, wherein the metal salt is at least one of a chloride salt, a gluconate salt, a citrate salt, a lactate salt, a malate salt, an aspartate salt, a fumarate salt, an ascorbate salt, a benzoate salt, an erythorbate salt and a propionate salt.

28. The method of claim 23, wherein the metal salt solution contains at least one of calcium, magnesium, cobalt, iron (2+), manganese, copper and zinc.

29. A method for suppressing or reducing the anti-coagulation effect of an oligonucleotide administration to a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

30. A method for suppressing or reducing subcutaneous injection site reactions of an oligonucleotide administration to a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

31. A method for improving the tolerability of an oligonucleotide when administered by IV infusion to a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

32. A method of reducing serum protein interaction of an oligonucleotide when administered by IV infusion to a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

33. A method of reducing the serum ½ life of an oligonucleotide in a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

34. A method of reducing liver or kidney dysfunction associated with oligonucleotide administration to a subject comprising the step of administering said oligonucleotide to the subject as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

35. A method of stabilizing an oligonucleotide in an aqueous solution comprising preparing said oligonucleotide as a chelate complex according to any one of claims 1-17, an oligonucleotide formulation according to any one of claims 18-21, or a pharmaceutical composition according to claim 22.

36. The method of any one of claims 23-35, wherein said chelate complex is a calcium chelate complex.

~~37. The method of any one of claims 23-35, wherein said chelate complex is a magnesium chelate complex.~~

~~38. The method of any one of claims 23-35, wherein said chelate complex is a mixed magnesium/calcium chelate complex.~~

~~39. Use of a multivalent cation in the manufacture of an oligonucleotide chelate complex, wherein said complex contains at least one oligonucleotide having at least one phosphorothioate linkage.~~

~~40. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, for suppressing or reducing the anti-coagulation effect of said oligonucleotide administration to a subject.~~

~~41. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, for suppressing or reducing subcutaneous injection site reactions in a subject of said subcutaneously administered oligonucleotide.~~

~~42. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, for improving the tolerability of said oligonucleotide in a subject when administered by IV infusion.~~

~~43. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, for reducing serum protein interaction of an oligonucleotide when administered by IV infusion to a subject.~~

~~44. Use the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical composition of claim 22, for reducing the serum half life of said oligonucleotide in a subject.~~

~~45. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21, or pharmaceutical~~

~~composition of claim 22, for reducing liver or kidney dysfunction associated with said oligonucleotide administration in a subject.~~

~~46. Use of the oligonucleotide chelate complex of any one of claims 1-17, the oligonucleotide formulation of any one of claims 18-21 , or pharmaceutical composition of claim 22, for the stabilization of an oligonucleotide in an aqueous solution.~~

~~47. The use of any one of claims 40-46, comprising an oligonucleotide calcium chelate complex.~~

~~48. The use of any one of claims 40-46, comprising an oligonucleotide magnesium chelate complex.~~

~~49. The use of any one of claims 40-46, comprising a mixed calcium/magnesium oligonucleotide chelate complex.~~

1. A pharmaceutical composition comprising an oligonucleotide chelate complex comprising:
at least two oligonucleotides linked intermolecularly by a divalent cation, wherein at least one oligonucleotide has at least one phosphorothioate linkage; and
a pharmaceutically acceptable excipient.

2. The oligonucleotide chelate complex of claim 1, wherein said divalent cation is an alkali earth metal with a 2+ charge state.

3. The oligonucleotide chelate complex of claim 1, wherein said divalent metal cation is a transition metal with a 2+ charge state.

4. The oligonucleotide chelate complex of claim 1, wherein said divalent metal cation is a lanthanide metal with a 2+ charge state.

5. The oligonucleotide chelate complex of claim 1, wherein said divalent metal cation is a post-transition metal with a 2+ charge state.

6. The oligonucleotide chelate complex of claim 1, wherein said divalent metal cation is calcium, magnesium, cobalt, iron (2+), manganese, copper or zinc.

7. The pharmaceutical composition of claim 1, wherein said oligonucleotide chelate complex comprises two or more different divalent metal cations.

8. The pharmaceutical composition of claim 1, wherein said oligonucleotide chelate complex comprises at least one double stranded oligonucleotide.

9. The pharmaceutical composition of claim 1, wherein said oligonucleotide chelate complex comprises at least one fully phosphorothioated oligonucleotide.

10. The pharmaceutical composition of claim 1, wherein said oligonucleotide chelate complex comprises at least one oligonucleotide with one 2′ modified ribose.

11. The pharmaceutical composition of claim 1, wherein said oligonucleotide chelate complex comprises at least one oligonucleotide which has each ribose 2′ O-methylated.

12. The pharmaceutical composition of claim 1 adapted for subcutaneous administration.

13. The pharmaceutical composition of claim 1, adapted for intravenous infusion.

14. The oligonucleotide chelate complex of claim 1, wherein said at least one oligonucleotide consists of a sequence selected from the group consisting of SEQ ID NOs: 3 to 14.

15. An oligonucleotide formulation for subcutaneous administration, said oligonucleotide formulation comprising the pharmaceutical composition of claim 1.

16. The formulation of claim 15 further adapted for subcutaneous administration.

17. The formulation of claim 15, wherein said formulation is further adapted for intravenous infusion.

18. The pharmaceutical composition of claim 1, wherein said at least one oligonucleotide comprises at least one 5-methylcytosine.

19. The pharmaceutical composition of claim 1, wherein said at least one oligonucleotide consists of SEQ ID NO: 6 comprising at least one 5-methylcytosine.

20. The pharmaceutical composition of claim 1, wherein said at least one oligonucleotide consists of SEQ ID NO: 6 wherein each cytosine is 5-methylcytosine.