mismatches to a target sequence of the partially processed mRNA transcript. In some instances, the polynucleic acid polymer is between about 10 and about 50, about 10 and about 45, about 10 and about 40, about 10 and about 30, about 10 and about 25, or about 10 and about 20 nucleotides in length.

[0034] In some instances, the subject is a eukaryote. In some instances, the subject is a eukaryote selected from a human, mouse, rat, non-human primate, or non-primate mammal.

[0035] In some aspects, described is a pharmaceutical composition which comprises a polynucleic acid polymer that hybridizes to a target sequence of a partially processed mRNA transcript which encodes a protein and which comprises a retained intron, wherein the polynucleic acid polymer induces splicing out of the retained intron from the partially processed mRNA transcript; and a pharmaceutically acceptable excipient and/or a delivery vehicle.

[0035a] In some aspects, the invention discloses a pharmaceutical composition comprising:
a polynucleic acid polymer that hybridizes to a target sequence of a partially processed mRNA transcript which encodes a protein and which comprises a retained intron, wherein the polynucleic acid polymer induces splicing out of the retained intron from the partially processed mRNA transcript, wherein the target region of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, and wherein the partially processed mRNA transcript comprising the target sequence encodes a full-length form of a protein; and
a pharmaceutically acceptable excipient and/or a delivery vehicle.

[0035b] In some aspects, the invention discloses the use of a pharmaceutical composition as described herein for the manufacture of a medicament for the treatment of a disease or condition comprising correction of intron retention in gene transcripts, wherein the disease or condition is diabetes, a hereditary disease, or cancer.

[0035c] In some aspects, the invention discloses the use of an isolated polynucleic acid polymer for the manufacture of a medicament for use in an *in vivo* method of inducing processing of a partially processed mRNA transcript to facilitate removal of a retained intron to produce a fully processed mRNA transcript that encodes a functional form of a protein and to treat a diabetes, a hereditary disease, or cancer, wherein said isolated polynucleic acid polymer hybridizes to a target sequence of the partially processed mRNA transcript, wherein the target sequence of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, wherein the partially processed mRNA transcript is capable of encoding the full-length functional form of a protein and comprises at least one retained intron, optionally interfering with one or more conformational

transitions of canonical and noncanonical RNA structures or interacting with trans-acting factors that bind to an intron; and wherein removing the at least one retained intron from the partially processed mRNA transcript produce the fully processed mRNA transcript that encodes the full-length functional form of a protein.

[0035d] In some aspects, the invention discloses the Use of a pharmaceutical composition for the manufacture of a medicament for the treatment or prevention of a disease or condition in a subject comprising correction of intron retention in gene transcripts, said pharmaceutical composition comprising: a polynucleic acid polymer that hybridizes to a target sequence of a partially processed mRNA transcript, wherein the partially processed mRNA transcript encodes a protein and comprises an entire retained intron, wherein the polynucleic acid polymer induces splicing out of the entire retained intron from the partially processed mRNA transcript, wherein the target region of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, and wherein the partially processed mRNA transcript comprising the target sequence encodes a full-length form of a protein; and a pharmaceutically acceptable excipient and/or a delivery vehicle; wherein the disease or condition is diabetes, a hereditary disease, or cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0037] Figure 1. Location of SSOs in the human proinsulin gene. (**A**) Schematics of the *INS* reporter and its mRNA products. SSOs are shown as black horizontal bars below exons (numbered boxes) and below intron 1 (line); their sequences are in Table 2. Start and stop codons are denoted by arrowheads. Canonical (solid lines) and cryptic (dotted lines) splicing is shown above the primary transcript; designation of cryptic splice sites is in grey. SSOs targeting intron 1 segments del4-del7 are shown in the lower panel. (**B**) mRNA isoforms (numbered 1–6) generated by the *INS* reporter construct. Description of isoforms that do not produce proinsulin is labelled with *.

[0038] Figure 2. SSO-induced inhibition of *INS* intron 1 retention. (**A**) Cotransfection of the *INS* reporter construct (IC D-F) with the indicated SSOs into HEK293 cells. Spliced products described in Figure 1B are shown to the right. Bars represent percentage of intron 1-containing isoforms relative to natural transcripts (upper panel) or percentage of splicing to the cryptic 3' splice site of

intron 2 relative to the total (lower panel). Error bars denote SD; sc, scrambled control; SSO-, 'no SSO' control. Final concentration of SSOs was 1, 3, 10 and 30 nM, except for SSO6 and SSO8 (10 and 30 nM). (**B**) SSO21-mediated promotion of intron 1 splicing in clones lacking the cryptic 3ss of intron 2. RNA products are to the right. (**C**) A fold change in SSO21-induced intron 1 retention in

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a polynucleic acid polymer that hybridizes to a target sequence of a partially processed mRNA transcript which encodes a protein and which comprises a retained intron, wherein the polynucleic acid polymer induces splicing out of the retained intron from the partially processed mRNA transcript, wherein the target region of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, and wherein the partially processed mRNA transcript comprising the target sequence encodes a full-length form of a protein; and

a pharmaceutically acceptable excipient and/or a delivery vehicle.

2. The pharmaceutical composition of claim 1, wherein the target sequence is a binding motif that forms a hairpin structure.
3. The pharmaceutical composition of claim 1, wherein the target sequence is in between two G quadruplexes of a partially processed mRNA transcript.
4. The pharmaceutical composition of claim 1, wherein the polynucleic acid polymer specifically hybridizes to the retained intron of the partially processed mRNA transcript.
5. The pharmaceutical composition of claim 1, wherein the target sequence does not form a G quadruplex.
6. The pharmaceutical composition of claim 1, wherein the target sequence is an intronic splicing regulatory element of the partially processed mRNA transcript.
7. The pharmaceutical composition of claim 6, wherein the intronic splicing regulatory element comprises a first CCC motif or a second CCC motif.
8. The pharmaceutical composition of claim 7, wherein the first CCC motif is about 3 or more nucleotide bases from the second CCC motif.
9. The pharmaceutical composition of claim 6, wherein the intronic splicing regulatory element comprises a CCCAG or an AGGCC motif.
10. The pharmaceutical composition of claim 1, wherein the delivery vehicle comprises a cell penetrating peptide or a peptide-based nanoparticle.

11. The pharmaceutical composition of claim 1, wherein the polynucleic acid polymer is between about 10 and about 50 nucleotides in length.

12. The pharmaceutical composition of claim 1, wherein the polynucleic acid polymer is between about 10 and about 30 nucleotides in length.

13. The pharmaceutical composition of claim 1, wherein the sequence of the polynucleic acid polymer is at least 60% complementary to a target sequence of the partially processed mRNA transcript.

14. The pharmaceutical composition of claim 1, wherein the polynucleic acid polymer is modified at the nucleoside moiety, at the phosphate moiety, at the 5' terminus, at the 3' terminus, or a combination thereof.

15. The pharmaceutical composition of claim 14, wherein the polynucleic acid polymer comprises one or more artificial nucleotide bases.

16. The pharmaceutical composition of claim 15, wherein the one or more artificial nucleotide bases comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified, locked nucleic acid (LNA), ethylene nucleic acid (ENA), peptide nucleic acid (PNA), 1', 5'- anhydrohexitol nucleic acids (HNA), morpholino, methylphosphonate nucleotides, thiolphosphonate nucleotides, or 2'-fluoro N3-P5'-phosphoramidites.

17. The pharmaceutical composition of claim 1, wherein the polynucleic acid polymer hybridizes to a mRNA transcript comprising:

    i) at least 80% sequence identity to at least 13 contiguous bases of SEQ ID NO: 46;

    ii) at least 10 contiguous bases of SEQ ID NO: 46;

    iii) at least 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 18, SEQ ID NO: 21, SEQ ID NO: 24, SEQ ID NO: 27, SEQ ID NO: 30, SEQ ID NO: 33, SEQ ID NO: 36, SEQ ID NO: 39, SEQ ID NO: 42, SEQ ID NO: 45, or combinations thereof;

    iv) at least 60% sequence identity to SEQ ID NO: 3; or

v) at least 80% sequence identity to at least 13 contiguous bases of a sequence selected from the group consisting of SEQ ID NOs: 47-434, or combinations thereof.

18. Use of a pharmaceutical composition of claims 1-17 for the manufacture of a medicament for the treatment of a disease or condition comprising correction of intron retention in gene transcripts, wherein the disease or condition is diabetes, a hereditary disease, or cancer.

19. Use of an isolated polynucleic acid polymer for the manufacture of a medicament for use in an *in vivo* method of inducing processing of a partially processed mRNA transcript to facilitate removal of a retained intron to produce a fully processed mRNA transcript that encodes a functional form of a protein and to treat a diabetes, a hereditary disease, or cancer, wherein

said isolated polynucleic acid polymer hybridizes to a target sequence of the partially processed mRNA transcript, wherein the target sequence of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, wherein the partially processed mRNA transcript is capable of encoding the full-length functional form of a protein and comprises at least one retained intron, optionally interfering with one or more conformational transitions of canonical and noncanonical RNA structures or interacting with trans-acting factors that bind to an intron; and wherein removing the at least one retained intron from the partially processed mRNA transcript produce the fully processed mRNA transcript that encodes the full-length functional form of a protein.

20. The use of claim 19, wherein the intron of step (b) is an *INS* intron.

21. The use of claim 19, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.

22. The use of claim 19, wherein the polynucleic acid polymer comprises an artificial nucleotide.

23. The use of claim 22, wherein the artificial nucleotide is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), 1',5'- anhydrohexitol nucleic acid (HNA), a

morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.

24. The use of claim 19, wherein the target sequence is a binding motif that forms a hairpin structure.

25. The use of claim 19, wherein the target sequence is between two G quadruplexes of a partially processed mRNA transcript.

26. The use of claim 19, wherein the target sequence is within the retained intron of the partially processed mRNA transcript.

27. The use of claim 19, wherein the target sequence does not form a G quadruplex.

28. The use of claim 19, wherein the target sequence is an intronic sequence.

29. The use of claim 28, wherein the intronic sequence comprises an intronic splicing regulatory element comprising a first CCC motif or a second CCC motif.

30. The use of claim 19, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length

31. The use of claim 19, wherein the polynucleic acid polymer is from about 10 to about 30 nucleotides in length.

32. The use of claim 19, wherein the polynucleic acid polymer comprises a sequence that is at least 60% complementary to the target sequence of the partially processed mRNA transcript.

33. The use of claim 19, wherein the polynucleic acid polymer comprises a sequence that is complementary to a sequence with:

    i) at least 80% sequence identity to at least 13 contiguous bases of SEQ ID NO: 46;

    ii) at least 10 contiguous bases of SEQ ID NO: 46;

    iii) at least 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQID NO: 18, SEQ ID NO: 21, SEQ ID NO: 24, SEQ ID NO: 27, SEQ ID NO: 30, SEQID NO: 33, SEQ ID NO: 36, SEQ ID NO: 39, SEQ ID NO: 42, and SEQ ID NO: 45;

    iv) at least 60% sequence identity to SEQ ID NO: 3; or

    v) at least 80% sequence identity to at least 13 contiguous bases of a sequence selected from the group consisting of SEQ ID NOs: 47-434.

34. The use of claim 19, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.

35. The use of any one of the claims 19-34, wherein the retained intron is an entire retained intron.

36. Use of a pharmaceutical composition for the manufacture of a medicament for the treatment or prevention of a disease or condition in a subject comprising correction of intron retention in gene transcripts, said pharmaceutical composition comprising:

(i) a polynucleic acid polymer that hybridizes to a target sequence of a partially processed mRNA transcript, wherein the partially processed mRNA transcript encodes a protein and comprises an entire retained intron, wherein the polynucleic acid polymer induces splicing out of the entire retained intron from the partially processed mRNA transcript, wherein the target region of the partially processed mRNA transcript does not comprise a mutation-induced aberrant splice site, and wherein the partially processed mRNA transcript comprising the target sequence encodes a full-length form of a protein; and

(ii) a pharmaceutically acceptable excipient and/or a delivery vehicle;

wherein the disease or condition is diabetes, a hereditary disease, or cancer.

37. The use of claim 36, wherein the therapeutic agent is a polynucleic acid polymer that is an anti-sense sequence that hybridizes to a retained intron of the partially processed mRNA transcript.

38. The use of claim 36, wherein the target sequence is a binding motif that forms a hairpin structure.

39. The use of claim 36, wherein the target sequence is between two G quadruplexes of a partially processed mRNA transcript.

40. The use of claim 36, wherein the target sequence is within the entire retained intron of the partially processed mRNA transcript.

41. The use of claim 36, wherein the target sequence does not form a G quadruplex.

42. The use of claim 36, wherein the target sequence is an intronic splicing regulatory element of the partially processed mRNA transcript.

43. The use of claim 42, wherein the intronic splicing regulatory element comprises a first CCC motif or a second CCC motif.

44. The use of claim 36, wherein the polynucleic acid polymer is from about 10 to about 50 nucleotides in length.

45. The use of claim 36, wherein the polynucleic acid polymer is from about 10 to about 30 nucleotides in length.

46. The use of claim 36, wherein the polynucleic acid polymer comprises a sequence that is at least 60% complementary to the target sequence of the partially processed mRNA transcript.

47. The use of claim 36, wherein the polynucleic acid polymer is modified at a nucleoside moiety, at a phosphate moiety, at a 5' terminus, at a 3' terminus, or a combination thereof.

48. The use of claim 47, wherein the polynucleic acid polymer comprises an artificial nucleotide.

49. The use of claim 48, wherein the artificial nucleotide is selected from the group consisting of 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, T-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), T-O- dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), a locked nucleic acid (LNA), an ethylene nucleic acid (ENA), a peptide nucleic acid (PNA), a 1',5'- anhydrohexitol nucleic acid (HNA), a morpholino, a methylphosphonate nucleotide, a thiolphosphonate nucleotide, and a 2'-fluoro N3-P5'-phosphoramidite.

50. The use of claim 36, wherein the polynucleic acid polymer hybridizes to a mRNA transcript comprising a sequence with:

i) at least 80% sequence identity to at least 13 contiguous bases of SEQ ID NO: 46;

ii) at least 10 contiguous bases of SEQ ID NO: 46;

iii) at least 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQID NO: 18, SEQ ID NO: 21, SEQ ID NO: 24, SEQ ID NO: 27, SEQ ID NO: 30, SEQID NO: 33, SEQ ID NO: 36, SEQ ID NO: 39, SEQ ID NO: 42, and SEQ ID NO: 45;

iv) at least 60% sequence identity to SEQ ID NO: 3; or

v) at least 80% sequence identity to at least 13 contiguous bases of a sequence selected from the group consisting of SEQ ID NOs: 47-434.

51. The use of claim 36, wherein the delivery vehicle comprises a cell penetrating peptide or a peptide-based nanoparticle.