The present disclosure provides meroduplex (nicked or gapped) ribonucleic acid molecules (mRNA) that decreases or silences target gene expression. An mRNA of this disclosure comprises at least three strands that combine to form at least two non-overlapping double-stranded regions separated by a nick or gap wherein one strand is complementary to a target gene RNA. In addition, the meroduplex may have one or more modifications or substitutions, such as nucleotide base, sugar, terminal cap structure, internucleotide linkage, or any combination of such modifications. Also provided are methods of decreasing expression of a target gene in a cell or in a subject to treat a disease related to altered expression of a target gene.
WHAT IS CLAIMED IS:

1. A ribonucleic acid comprising an A strand, which is complementary to a target RNA, the A strand having a length from 15 to 30 nucleotides, an S1 strand having a length from 5 to 25 nucleotides, and an S2 strand having a length from 5 to 25 nucleotides, wherein:
   (a) the S1 strand and the A strand anneal to form a first double-stranded region from 5 to 13 base pairs in length;
   (b) the S2 strand and the A strand anneal to form a second double-stranded region;
   (c) the first double-stranded region is separated from the second double-stranded region by a gap, the gap being from 1 to 10 unpaired nucleotides of the A strand, and the gap is between the first double-stranded region and the second double-stranded region; and
   (d) the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 5 nucleotides in length.

2. A ribonucleic acid comprising an A strand, an S1 strand, and an S2 strand, wherein:
   the A strand is an antisense strand having a length from 18 to 25 nucleotides;
   the S1 strand has a length from 5 to 15 nucleotides;
   the S2 strand has a length from 3 to 13 nucleotides;
   the sum of the lengths of the S1 strand and the S2 strand is from 18 to 25 nucleotides;
   the A strand, S1 strand, and S2 strand form a first double-stranded region and a second double-stranded region;
   the first double-stranded region is spaced apart from the second double-stranded region by a gap, the gap being a single-stranded region of the A strand between the first double-stranded region and the second double-stranded region, wherein the gap is from 1 to 10 nucleotides in length; and
   the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 4 nucleotides in length.
3. A ribonucleic acid comprising an A strand, which is complementary to a target RNA, the A strand having a length from 16 to 30 nucleotides, an S1 strand having a length from 5 to 25 nucleotides, and an S2 strand having a length from 15 to 25 nucleotides, wherein:

(a) the S1 strand and the A strand anneal to form a first double-stranded region;
(b) the S2 strand and the A strand anneal to form a second double-stranded region;
(c) at least one double-stranded region is from 5 base pairs to 13 base pairs in length;
(d) the first double-stranded region is separated from the second double-stranded region by a gap, the gap being from 1 to 10 unpaired nucleotides of the A strand, and the gap is between the first double-stranded region and the second double-stranded region; and
(e) the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 5 nucleotides in length.

4. A ribonucleic acid comprising an A strand, which is complementary to a target RNA, the A strand having a length from 15 to 30 nucleotides, an S1 strand having a length from 6 to 25 nucleotides, and an S2 strand having a length from 6 to 25 nucleotides, wherein:

(a) the S1 strand and the A strand anneal to form a first double-stranded region from 5 to 13 base pairs in length;
(b) the S2 strand and the A strand anneal to form a second double-stranded region;
(c) the ribonucleic acid has a nick between the first double-stranded region and the second double-stranded region; and
(d) the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 5 nucleotides in length.

5. A ribonucleic acid comprising an A strand, an S1 strand, and an S2 strand, wherein:
the A strand is an antisense strand having a length from 18 to 25 nucleotides;
the S1 strand has a length from 5 to 15 nucleotides;
the S2 strand has a length from 3 to 13 nucleotides or less;
the sum of the lengths of the S1 strand and the S2 strand is from 18 to 25 nucleotides;
the A strand, S1 strand, and S2 strand form a first double-stranded region and a second double-stranded region;
the ribonucleic acid has a nick between the first double-stranded region and the second double-stranded region; and
the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 4 nucleotides in length.

6. A ribonucleic acid comprising an A strand, which is complementary to a target RNA, the A strand having a length from 16 to 30 nucleotides, an S1 strand having a length from 5 to 25 nucleotides, and an S2 strand having a length from 15 to 25 nucleotides, wherein:
   (a) the S1 strand and the A strand anneal to form a first double-stranded region;
   (b) the S2 strand and the A strand anneal to form a second double-stranded region;
   (c) at least one double-stranded region is from 5 base pairs to 13 base pairs in length;
   (d) the ribonucleic acid has a nick between the first double-stranded region and the second double-stranded region; and
   (e) the ribonucleic acid has 0, 1, or 2 overhangs, wherein the overhangs are not in the gap and each are independently from 1 to 5 nucleotides in length.

7. The ribonucleic acid of any one of claims 1-3, wherein the gap has a length of from 1 to 6 unpaired nucleotides.

8. The ribonucleic acid of any one of claims 1-3, wherein the gap has a length of 1 unpaired nucleotide.
9. The ribonucleic acid of any one of claims 1-6, wherein the overhangs are 3' overhangs, and each overhang has a length of from 1 to 4 nucleotides.

10. The ribonucleic acid of any one of claims 1-6, wherein a 3'-end that is not part of the gap of the ribonucleic acid is a blunt end.

11. The ribonucleic acid of any one of claims 1-6, wherein the A strand has a length of from 19 to 25 nucleotides.

12. The ribonucleic acid of any one of claims 1-6, wherein the A strand has a length of from 25 to 30 nucleotides.

13. The ribonucleic acid of any one of claims 1-6, wherein the sum of the lengths of the first double-stranded region and the second double-stranded region is from 19 to 25 base pairs.

14. The ribonucleic acid of any one of claims 1-6, wherein the sum of the lengths of the first double-stranded region and the second double-stranded region is from 25 to 30 base pairs.

15. The ribonucleic acid of any one of claims 1-6, wherein at least one nucleotide has a modified sugar.

16. The ribonucleic acid of any one of claims 1-6, wherein at least one nucleotide has a 2' sugar bridge.

17. The ribonucleic acid of any one of claims 1-6, wherein at least one nucleotide has a modified internucleoside linkage.

18. The ribonucleic acid of any one of claims 1-6, wherein at least one nucleotide is a locked nucleic acid nucleotide.

19. The ribonucleic acid of any one of claims 1-6, wherein at least one nucleotide is a locked nucleic acid nucleotide, or at least one nucleotide has a 2'-sugar substitution, or at least one nucleotide has a G clamp, or at least one nucleotide has a modified internucleoside linkage, or at least one nucleotide has a terminal cap substituent, at least one nucleotide has a 2'-methoxy or fluoro modification, or at least
one nucleotide has a phosphorothioate intemucleoside linkage, or any combination thereof.

20. The ribonucleic acid of any one of claims 1-6, wherein at least one pyrimidine of the ribonucleic acid comprises a pyrimidine nucleoside according to Formula I or II:

\[
\text{(I)} \quad R^1 \quad R^2 \quad R^3 \quad R^4
\]
\[
\text{(II)} \quad R^1 \quad R^2 \quad R^3 \quad R^4
\]

wherein:

- \( R^1 \) and \( R^2 \) are each independently a -H, -OH, -OCH\(_3\), -OCH\(_2\)OCH\(_2\)CH\(_3\), -OCH\(_2\)CH\(_2\)OCH\(_3\), halogen, substituted or unsubstituted \( C_1-C_{10} \) alkyl, alkoxy, alkoxyalkyl, hydroxyalkyl, carboxyalkyl, alkylsulfonylamino, aminoalkyl, dialkylamino, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, trifluoromethyl, cycloalkyl, (cycloalkyl)alkyl, substituted or unsubstituted \( C_2-C_{10} \) alkenyl, substituted or unsubstituted \(-O\)-allyl, \(-O-CH\_2CH=CH\_2\), \(-O-CH=CHCH\_3\), substituted or unsubstituted \( C_2-C_{10} \) alkynyl, carbamoyl, carbamyl, carboxy, carbamylamino, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, \(-NH\_2\), \(-NO\_2\), \(-C\equivN\), or heterocyclo group.

- \( R^3 \) and \( R^4 \) are each independently a hydroxyl, a protected hydroxyl, a phosphate, or an intemucleoside linking group, and

- \( R^5 \) and \( R^8 \) are independently \( O \) or \( S \).

21. The ribonucleic acid of claim 20, wherein at least one nucleoside is according to Formula I in which \( R^1 \) is methyl and \( R^2 \) is -OH.

22. The ribonucleic acid of claim 20, wherein at least one nucleoside is according to Formula I in which \( R^2 \) is -OCH\(_2\) or fluoro.
23. A pharmaceutical composition comprising the ribonucleic acid according to any one of claims 1-22 and a pharmaceutically acceptable carrier, diluent, excipient, adjuvant, emulsifier, buffer, stabilizer, or preservative.

24. The pharmaceutical composition of claim 23 further comprising a liposome, a hydrogel, a cyclodextrin, a biodegradable nanocapsule, a bioadhesive microsphere, or a proteinaceous vector.

25. A method for reducing the expression of a target gene in a cell expressing the mRNA of the target gene, comprising administering the ribonucleic acid according to any one of claims 1-22 to the cell.

26. The method according to claim 25, wherein the cell is a human cell.

27. A method for treating a hyperproliferative or inflammatory disease by reducing the expression of a target RNA, comprising administering the ribonucleic acid according to any one of claims 1-22 to a human subject expressing the target RNA.

28. A method for treating an infectious disease, comprising administering the ribonucleic acid according to any one of claims 1-22 to an infected human subject, wherein the ribonucleic acid reduces expression of a target RNA of a microorganism infecting the human subject.

29. The use of the ribonucleic acid as in any one of claims 1-22 as a medicament in treating a hyperproliferative, inflammatory, or infectious disease in a human subject.

30. The use of the ribonucleic acid as in any one of claims 1-22 for the manufacture of a medicament for use in the therapy for a human subject of a hyperproliferative, inflammatory, or infectious disease.