miRNA sequences of the duplex within pre-miRNAs [Tiwari et al. (2014) supra]. These amiRNAs are introduced as a transgene within an artificial expression cassette (including a promoter, terminator etc.) [Carbonell et al., *Plant Physiology* (2014) pp.113.234989], are processed via small RNA biogenesis and silencing machinery and downregulate target expression. According to Schwab et al. [Schwab et al. *The Plant Cell* (2006) Vol. 18, 1121–1133], amiRNAs are active when expressed under tissue-specific or inducible promoters and can be used for specific gene silencing in plants, especially when several related, but not identical, target genes need to be downregulated.

Senis et al. [Senis et al., *Nucleic Acids Research* (2017) Vol. 45(1): e3] disclose engineering of a promoterless anti-viral RNAi hairpin into an endogenous miRNA locus. Specifically, Senis et al. insert an amiRNA precursor transgene (hairpin pri-amiRNA) adjacent to a naturally occurring miRNA gene (e.g. miR122) by homology-directed DNA recombination that is induced by sequence-specific nuclease such as Cas9 or TALEN nucleases. This approach uses promoter- and terminator-free amiRNAs by utilizing transcriptionally active DNA that expresses a natural miRNA (miR122), that is, the endogenous promoter and terminator drove and regulated the transcription of the inserted amiRNA transgene.

Various DNA-free methods of introducing RNA and/or proteins into cells have been previously described. For example, RNA transfection using electroporation and lipofection has been described in U.S. Patent Application No. 20160289675. Direct delivery of Cas9/sgRNA ribonucleoprotein (RNPs) complexes to cells by microinjection of the Cas9 protein and sgRNA complexes was described by Cho [Cho et al., "Heritable gene knockout in Caenorhabditis elegans by direct injection of Cas9-sgRNA ribonucleoproteins," *Genetics* (2013) 195:1177-1180]. Delivery of Cas9 protein/sgRNA complexes via electroporation was described by Kim [Kim et al., "Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins" *Genome Res.* (2014) 24:1012-1019]. Delivery of Cas9 protein-associated sgRNA complexes via liposomes was reported by Zuris [Zuris et al., "Cationic lipid-mediated delivery of proteins enables efficient protein-based genome editing in vitro and in vivo" *Nat Biotechnol.* (2014) doi: 10.1038/nbt.3081].

SUMMARY

In one aspect, the present disclosre refers to a method of generating an RNA molecule having a silencing activity in a cell, the method comprising:

(a) identifying a nucleic acid sequence that:

i. encodes an RNA molecule exhibiting a predetermined sequence homology range, not including complete identity, with respect to a nucleic acid sequence encoding an RNA molecule engaged with RNA-induced silencing complex (RISC);

ii. is determined to be transcribable; and

iii. encodes an RNA molecule determined to be aberrantly processed; and

(b) modifying said nucleic acid sequence so as to impart processability into small RNAs that are engaged with RISC and are complementary to a first target RNA,

thereby generating the RNA molecule having the silencing activity in the cell

In another aspect, the present disclosure refers to a genetically modified cell comprising a genome comprising a polynucleotide sequence encoding an RNA molecule having a nucleic acid sequence alteration which results in processing of said RNA molecules into small RNAs that are engaged with RISC, said processing of said RNA molecules being absent from a wild type cell of the same origin devoid of said nucleic acid sequence alteration.

In another aspec, the present disclosure refers to a plant cell generated according to the method as disclosed herein.

In another aspect, the present disclosure refers to a method of producing a plant with reduced expression of a target gene, the method comprising:

(a) breeding the plant as disclosed herein; and

(b) selecting for progeny plants that have reduced expression of said target RNA of interest, or progeny that comprise a silencing specificity in said RNA molecule towards said target RNA of interest, and which do not comprise said DNA editing agent,

thereby producing said plant with reduced expression of a target gene.

In yet another aspect, the present disclosure refers to a method of producing a plant comprising an RNA molecule having a silencing activity towards a target RNA of interest, the method comprising:

(a) breeding the plant as disclosed herein; and

(b) selecting for progeny plants that comprise said RNA molecule having said silencing activity towards said target RNA of interest, or progeny that comprise a silencing specificity in said RNA molecule towards said target RNA of interest, and which do not comprise said DNA editing agent,

thereby producing the plant comprising the RNA molecule having the silencing activity towards the target RNA of interest.

In yet another aspect, the present disclosure refers to a method of producing a plant or plant cell as disclosed herein comprising growing the plant or plant cell under conditions which allow propagation.

In yet another aspect, the present disclosure refers to a seed of the plant as disclosed herein, or of the plant produced by the method as disclosed herein.

In yet another aspect, the present disclosure refers to a DNA editing agent for use in treating a disease in a subject in need thereof, comprising generating an RNA molecule having a silencing activity and/or specificity according to the method as disclosed herein, wherein said RNA molecule comprises a silencing activity towards a transcript of a gene associated with an onset or progression of the disease, thereby treating the subject.

In yet another aspect, the present disclosure refers to a method of introducing silencing activity to a first RNA molecule in a cell, the method comprising:

(a) selecting a first nucleic acid sequence within said cell, wherein:

i. said first nucleic acid sequence is transcribed into said first RNA molecule within the cell;

ii. the sequence of said first RNA molecule has a partial homology to the sequence of a second RNA molecule, excluding sequence identity; wherein said second RNA molecule is processable to a third RNA molecule having a silencing activity; and wherein said second RNA molecule is encoded by a second nucleic acid sequence in said cell; and

iii. said first RNA molecule is not processable, or is processable differently than the second RNA molecule, such that the first RNA molecule is not processed to an RNA molecule having a silencing activity of the same nature as the third RNA molecule;

(b) modifying the first nucleic acid sequence such that it encodes a modified first RNA molecule, said modified first RNA molecule being processable to a fourth RNA in the same way that said second RNA molecule is processable to the third RNA molecule, such that the fourth RNA molecule has a silencing activity of the same nature as the third RNA molecule,

thereby introducing a silencing activity to the first RNA molecule.

According to some examples of the present disclosure there is provided a method of generating an RNA molecule having a silencing activity in a cell, the method comprising: (a) identifying nucleic acid sequences encoding RNA molecules exhibiting a predetermined sequence homology range, not including complete identity, with respect to nucleic

acid sequences encoding RNA molecules engaged with RNA-induced silencing complex (RISC);

(b) determining transcription of the nucleic acid sequences encoding the RNA molecules so as to select transcribable nucleic acid sequences encoding the RNA molecules exhibiting the predetermined sequence homology range; (c) determining processability into small RNAs of transcripts of the transcribable nucleic acid sequences encoding the RNA molecules exhibiting the predetermined sequence homology range so as to select transcribable nucleic acid sequences encoding the RNA molecules exhibiting the predetermined sequence homology range, wherein the RNA molecules are aberrantly processed; (d) modifying a nucleic acid sequence of the transcribable nucleic acid sequences encoding the aberrantly processed RNA molecules exhibiting the predetermined sequence homology range so as to impart processability into small RNAs that are engaged with RISC and are complementary to a first target RNA, thereby generating the RNA molecule having the silencing activity in the cell.

According to some examples of the present disclosure there is provided a genetically modified cell comprising a genome comprising a polynucleotide sequence encoding an RNA molecule having a nucleic acid sequence alteration which results in processing of the RNA molecules into small RNAs that are engaged with RISC, the processing of the RNA molecules being absent from a wild type cell of the same origin devoid of the nucleic acid sequence alteration.

According to some examples of the present disclosure there is provided a plant cell generated according to the method of some examples of the disclosure.

According to some examples of the present disclosure there is provided a plant comprising the plant cell of some examples of the disclosure.

According to some examples of the present disclosure there is provided a method of producing a plant with reduced expression of a target gene, the method comprising: (a) breeding the plant of some examples of the disclosure; and (b) selecting for progeny plants that have reduced expression of the target RNA of interest, or progeny that comprise a silencing specificity in the RNA molecule towards the target RNA of interest, and which do not comprise the DNA editing agent, thereby producing the plant with reduced expression of a target gene.

According to some examples of the present disclosure there is provided a method of producing a plant comprising an RNA molecule having a silencing activity towards a target RNA of interest, the method comprising: (a) breeding the plant of some examples of the disclosure; and (b) selecting for progeny plants that comprise the RNA molecule having the silencing activity towards the target RNA of interest, or progeny that comprise a silencing specificity in the RNA molecule towards the target RNA of interest, and which do not comprise the DNA editing agent, thereby producing the plant comprising the RNA molecule having the silencing activity towards the target RNA of interest.

According to some examples of the present disclosure there is provided a method producing a plant or plant cell of some examples of the disclosure comprising growing the plant or plant cell under conditions which allow propagation.

According to some examples of the present disclosure there is provided a seed of the plant of some examples of the disclosure, or of the plant produced by some examples of the disclosure.

According to some examples of the present disclosure there is provided a method of treating a disease in a subject in need thereof, the method comprising generating an RNA molecule having a silencing activity and/or specificity according to the method of some examples of the disclosure, wherein the RNA molecule comprises a silencing activity towards a transcript of a gene associated with an onset or progression of the disease, thereby treating the subject.

According to some examples of the present disclosure there is provided a method of introducing silencing activity to a first RNA molecule in a cell, the method comprising:

(a) selecting a first nucleic acid sequence within the cell, wherein:

i. the first nucleic acid sequence is transcribed into the first RNA molecule within the cell;

ii. the sequence of the first RNA molecule has a partial homology to the sequence of a second RNA molecule, excluding sequence identity; wherein the second RNA molecule is processable to a third RNA molecule having a silencing activity; and wherein the second RNA molecule is encoded by a second nucleic acid sequence in the cell; and

iii. the first RNA molecule is not processable, or is processable differently than the second RNA molecule, such that the first RNA molecule is not processed to an RNA molecule having a silencing activity of the same nature as the third RNA molecule;

(b) modifying the first nucleic acid sequence such that it encodes a modified first RNA molecule, the modified first RNA molecule being processable to a fourth RNA in the same way that the second RNA molecule is processable to the third RNA molecule, such that the fourth RNA molecule has a silencing activity of the same nature as the third RNA molecule,

thereby introducing a silencing activity to the first RNA molecule.

According to some examples of the disclosure, the RNA molecules of step (a) encoded by the identified nucleic acid sequences exhibit a predetermined sequence homology range, not

including complete identity, with respect to RNA molecules that are engaged with- and/or that are processed into molecules engaged with RISC.

According to some examples of the disclosure, imparting processability in step (d) comprises imparting canonical processing relative to an RNA molecule encoded by a nucleic acid sequence of the nucleic acid sequences encoding RNA molecules engaged with RNA-induced silencing complex (RISC);

According to some examples of the disclosure, the method further comprises determining the genomic location of the nucleic acid sequences encoding the RNA molecules exhibiting the predetermined sequence homology range of step (a).

According to some examples of the disclosure, the genomic location is in a non-coding gene.

According to some examples of the disclosure, the genomic location is within an intron of a non-coding gene.

According to some examples of the disclosure, the genomic location is in a coding gene.

According to some examples of the disclosure, the genomic location is within an exon of coding gene.

According to some examples of the disclosure, the genomic location is within an exon encoding an untranslated region (UTR) of a coding gene.

According to some examples of the disclosure, the genomic location is within an intron of a coding gene.

According to some examples of the disclosure, the RNA molecule is encoded by a nucleic acid sequence positioned in a non-coding gene.

According to some examples of the disclosure, the RNA molecule is encoded by a nucleic acid sequence positioned in a coding gene.

According to some examples of the disclosure, the RNA molecule is encoded by a nucleic acid sequence positioned within an exon of coding gene.

According to some examples of the disclosure, the RNA molecule is encoded by a nucleic acid sequence positioned within an exon encoding an untranslated region (UTR) of coding gene.

According to some examples of the disclosure, the RNA molecule is encoded by a nucleic acid sequence positioned within an intron of coding gene.

According to some examples of the disclosure, the genomic location is within an intron of non-coding gene.

According to some examples of the disclosure, the sequence homology range comprises

75% - 99.6% identity with respect to the nucleic acid sequence encoding the RNA molecule engaged with the RISC.

According to some examples of the disclosure, step (b) and/or (c) are affected by alignment of small RNA expression data to a genome of the cell and determining the amount of reads that map to each genomic location.

According to some examples of the disclosure, the alignment of the small RNAs is alignment to a predetermined location in the genome of the cell with no mismatches.

According to some examples of the disclosure, modifying the nucleic acid sequence of the transcribable nucleic acid sequences imparts a structure of the aberrantly processed RNA molecules, which results in processing of the RNA molecules into small RNAs that are engaged with RISC.

According to some examples of the disclosure, modifying the nucleic acid sequence of the transcribable nucleic acid sequences encoding the aberrantly processed RNA molecules exhibiting the predetermined sequence homology range is affected at nucleic acids other than those corresponding to the binding site to the first target RNA.

According to some examples of the disclosure, the processability is affected by cellular nucleases selected from the group consisting of Dicer, Argonaute, tRNA cleavage enzymes, and Piwi-interacting RNA (piRNA) related proteins.

According to some examples of the disclosure, modifying in step (d) comprises introducing into the cell a DNA editing agent which reactivates silencing activity in the aberrantly processed RNA molecule towards the first target RNA, thereby generating an RNA molecule having a silencing activity in the cell.

According to some examples of the disclosure, the method further comprises modifying the specificity of the RNA molecule having the silencing activity in the cell, the method comprising introducing into the cell a DNA editing agent which redirects a silencing specificity of the RNA molecule towards a target RNA of interest, the target RNA of interest being distinct from the first target RNA, thereby modifying the specificity of the RNA molecule having the silencing activity in the cell.

According to some examples of the disclosure, the method further comprises modifying the specificity of the RNA molecule having the silencing activity in the cell, wherein the DNA editing agent redirects a silencing specificity of the RNA molecule towards a target RNA of interest, the target RNA of interest being distinct from the first target RNA, thereby modifying the specificity of the RNA molecule having the silencing activity in the cell.

According to some examples of the disclosure, the method further comprising modifying

the specificity of the RNA molecule having the silencing activity in a cell, the method comprising introducing into the cell a DNA editing agent which redirects a silencing specificity of the RNA molecule towards a target RNA of interest, the target RNA of interest being distinct from the first target RNA, thereby modifying the specificity of the RNA molecule having the silencing activity in the cell.

According to some examples of the disclosure, the identified nucleic acid sequences encoding RNA molecules of step (a) are homologous to genes encoding silencing RNA molecules whose silencing activity and/or processing into small silencing RNA is dependent on their secondary structure.

According to some examples of the disclosure, the nucleic acid sequences encoding RNA molecules of step (a) are homologous to genes encoding miRNA precursors.

According to some examples of the disclosure, the silencing RNA molecule whose silencing activity and/or processing into small silencing RNA is dependent on secondary structure is selected from the group consisting of: microRNA (miRNA), short-hairpin RNA (shRNA), small nuclear RNA (snRNA or U-RNA), small nucleolar RNA (snoRNA), Small Cajal body RNA (scaRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), repeat-derived RNA, autonomous and non-autonomous transposable and retro-transposable element-derived RNA, autonomous and non-autonomous transposable and retro-transposable element RNA and long non-coding RNA (lncRNA).

According to some examples of the disclosure, the processing is canonical processing.

According to some examples of the disclosure, the RNA molecule has a silencing activity.

According to some examples of the disclosure, the RNA molecule is selected from the group consisting of a microRNA (miRNA), a small interfering RNA (siRNA), a short hairpin RNA (shRNA), a Piwi-interacting RNA (piRNA), phased small interfering RNA (phasiRNA), trans-acting siRNA (tasiRNA), a transfer RNA fragment (tRF), a small nuclear RNA (snRNA), transposable and/or retro-transpossable derived RNA, autonomous and non-autonomous transposable and/or retro-transpossable RNA.

According to some examples of the disclosure, the method further comprises introducing into the cell donor oligonucleotides.

According to some examples of the disclosure, the DNA editing agent comprises at least one sgRNA.

According to some examples of the disclosure, the DNA editing agent does not comprise an endonuclease.

According to some examples of the disclosure, the DNA editing agent comprises an endonuclease.

According to some examples of the disclosure, the DNA editing agent is of a DNA editing system selected from the group consisting of a meganuclease, a zinc finger nucleases (ZFN), a transcription-activator like effector nuclease (TALEN), CRISPR-endonuclease, dCRISPR-endonuclease and a homing endonuclease.

According to some examples of the disclosure, the endonuclease comprises Cas9.

According to some examples of the disclosure, the DNA editing agent is applied to the cell as DNA, RNA or RNP.

According to some examples of the disclosure, the DNA editing agent is linked to a reporter for monitoring expression in a cell.

According to some examples of the disclosure, the reporter is a fluorescent protein.

According to some examples of the disclosure, the target RNA of interest is endogenous to the cell.

According to some examples of the disclosure, the target RNA of interest is exogenous to the cell.

According to some examples of the disclosure, the silencing specificity of the RNA molecule is determined by measuring a RNA or protein level of the target RNA of interest.

According to some examples of the disclosure, the silencing specificity of the RNA molecule is determined phenotypically.

According to some examples of the disclosure, the specificity of the RNA molecule is determined phenotypically by determination of at least one phenotype selected from the group consisting of a cell size, a growth rate/inhibition, a cell shape, a cell membrane integrity, a tumor size, a tumor shape, a pigmentation of an organism, a size of an organism, a crop yield, metabolic profile, a fruit trait, a biotic stress resistance, an abiotic stress resistance, an infection parameter, and an inflammation parameter.

According to some examples of the disclosure, the silencing specificity of the RNA molecule is determined genotypically.

According to some examples of the disclosure, the cell is a eukaryotic cell.

According to some examples of the disclosure, the eukaryotic cell is obtained from a eukaryotic organism selected from the group consisting of a plant, a mammal, an invertebrate, an insect, a nematode, a bird, a reptile, a fish, a crustacean, a fungi and an algae.

According to some examples of the disclosure, the eukaryotic cell is a plant cell.

According to some examples of the disclosure, the plant cell is a protoplast.

According to some examples of the disclosure, the plant is non-transgenic.

According to some examples of the disclosure, the plant is a transgenic plant.

According to some examples of the disclosure, the plant is non-genetically modified (non-GMO).

According to some examples of the disclosure, the plant is genetically modified (GMO).

According to some examples of the disclosure, the breeding comprises crossing or selfing.

According to some examples of the disclosure, the eukaryotic cell is a non-human animal cell.

According to some examples of the disclosure, the eukaryotic cell is a non-human mammalian cell.

According to some examples of the disclosure, the eukaryotic cell is a human cell.

According to some examples of the disclosure, the nucleic acid sequences encoding RNA molecules are selected from the group consisting of the nucleic acid sequences as set forth in any of SEQ ID NOs. 352 to 392.

According to some examples of the disclosure, the eukaryotic cell is a totipotent stem cell.

According to some examples of the disclosure, the gene associated with the onset or progression of the disease comprises a gene of a pathogen.

According to some examples of the disclosure, the gene associated with the onset or progression of the disease comprises a gene of the subject.

According to some examples of the disclosure, the disease is selected from the group consisting of an infectious disease, a monogenic recessive disorder, an autoimmune disease and a cancerous disease.

According to some examples of the disclosure, the second RNA molecule is an RNA molecule which has a secondary structure that enables it to be processed into an RNA having a silencing activity, optionally wherein the silencing activity is mediated through engaging RISC.

According to some examples of the disclosure, the RNA molecule which has a secondary structure that enables it to be processed into an RNA having a silencing activity is selected from the group consisting of: microRNA (miRNA), short-hairpin RNA (shRNA), small nuclear RNA (snRNA or URNA), small nucleolar RNA (snoRNA), Small Cajal body RNA (scaRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), repeat-derived RNA, autonomous and non-autonomous transposable and retro-transposable element-derived RNA, autonomous and non-

autonomous transposable and retro-transposable element RNA and long non-coding RNA (lncRNA).

According to some examples of the disclosure, the first nucleic acid sequence results in a secondary structure which enables the modified first RNA molecule to be processed into the fourth RNA molecule.

According to some examples of the disclosure, modifying the first nucleic acid sequence comprises modifying the sequence such that the modified first RNA molecule has essentially the same secondary structure as that of the second RNA molecule.

According to some examples, the secondary structure is at least 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or 100% identical to the secondary structure of the second RNA molecule (e.g. when the secondary structure of the first RNA molecule is translated to a linear string form and is compared to a string form of a secondary structure of the second RNA molecule).

According to some examples of the disclosure, the first nucleic acid molecule is a gene from *H. sapiens*, wherein the gene is selected from the group consisting of the genes having the sequences set forth in any of SEQ ID NOs. 352 to 392.

According to some examples of the disclosure, the subject is a human subject.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of examples of the disclosure, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIG. 1 is a flow chart of an embodiment computational pipeline for imparting a silencing activity of dysfunctional non-coding RNA molecules and redirecting their silencing specificity. Of note, a computational Genome Editing Induced Gene Silencing (GEiGS) pipeline applies biological

WHAT IS CLAIMED IS:

1. A method of generating an RNA molecule having a silencing activity in a cell, the method comprising:

(a) identifying a nucleic acid sequence that:

i. encodes an RNA molecule exhibiting a predetermined sequence homology range, not including complete identity, with respect to a nucleic acid sequence encoding an RNA molecule engaged with RNA-induced silencing complex (RISC);

ii. is determined to be transcribable; and

iii. encodes an RNA molecule determined to be aberrantly processed; and

(b) modifying said nucleic acid sequence so as to impart processability into small RNAs that are engaged with RISC and are complementary to a first target RNA,

thereby generating the RNA molecule having the silencing activity in the cell.

2. The method of claim 1, wherein:

(i) said RNA molecule of step (a) encoded by the identified nucleic acid sequence exhibits a predetermined sequence homology range, not including complete identity, with respect to an RNA molecule that is engaged with and/or that is processed into a molecule engaged with RISC; and/or

(ii) imparting processability in step (b) comprises imparting canonical processing relative to an RNA molecule encoded by a nucleic acid sequence of said nucleic acid sequence encoding RNA molecule engaged with RNA-induced silencing complex (RISC); and/or

(iii) wherein the method further comprises determining the genomic location of said nucleic acid sequence encoding said RNA molecule exhibiting said predetermined sequence homology range of step (a), optionally wherein:

(I) said genomic location is in a non-coding gene, optionally within an intron of a non-coding gene; or

(II) said genomic location is in a coding gene, optionally within an exon of coding gene, optionally within an exon encoding an untranslated region (UTR) of a coding gene, or optionally within an intron of a coding gene.

3. The method of claim 1 or 2, wherein:

(i) step (a) is affected by alignment of small RNA expression data to a genome of said cell and determining the amount of reads that map to each genomic location, optionally wherein said alignment of said small RNAs is alignment to a predetermined location in said genome of said cell

with no mismatches; and/or

(ii) said modifying said nucleic acid sequence of said transcribable nucleic acid sequence imparts a structure of said aberrantly processed RNA molecule, which results in processing of said RNA molecule into small RNAs that are engaged with RISC; and/or

(iii) said modifying said nucleic acid sequence of said transcribable nucleic acid sequence encoding said aberrantly processed RNA molecule exhibiting said predetermined sequence homology range is effected at nucleic acids other than those corresponding to the binding site to said first target RNA; and/or

(iv) said processability is effected by cellular nucleases selected from the group consisting of Dicer, Argonaute, tRNA cleavage enzymes, and Piwi-interacting RNA (piRNA) related proteins.

4. The method of any one of claims 1-3, wherein modifying in step (b) comprises introducing into the cell a DNA editing agent which reactivates silencing activity in said aberrantly processed RNA molecule towards said first target RNA, thereby generating an RNA molecule having a silencing activity in the cell.

5. The method of any one of claims 1-4, further comprising modifying the specificity of said RNA molecule having the silencing activity in the cell, wherein said DNA editing agent redirects a silencing specificity of said RNA molecule towards a target RNA of interest, said target RNA of interest being distinct from said first target RNA, thereby modifying said specificity of said RNA molecule having said silencing activity in said cell.

6. The method of any one of claims 1-5, wherein the identified nucleic acid sequence encoding the RNA molecule of step (a) is homologous to a gene encoding a silencing RNA molecule whose silencing activity and/or processing into small silencing RNA is dependent on its secondary structure, optionally wherein the silencing RNA molecule whose silencing activity and/or processing into small silencing RNA is dependent on secondary structure is selected from the group consisting of: microRNA (miRNA), short-hairpin RNA (shRNA), small nuclear RNA (snRNA or U-RNA), small nucleolar RNA (snoRNA), Small Cajal body RNA (scaRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), repeat-derived RNA, autonomous and non-autonomous transposable and retro-transposable element-derived RNA, autonomous and non-autonomous transposable and retro-transposable element RNA and long non-coding RNA (lncRNA).

7. A genetically modified cell comprising a genome comprising a polynucleotide sequence encoding an RNA molecule having a nucleic acid sequence alteration which results in processing of said RNA molecules into small RNAs that are engaged with RISC, said processing of said RNA molecules being absent from a wild type cell of the same origin devoid of said nucleic acid sequence alteration.

8. The genetically modificed cell of claim 7, wherein processing is canonical processing and/or wherein said RNA molecule has a silencing activity.

9. The method of any one of claims 1-5, or genetically modified cell of claim 7 or 8, wherein said RNA molecule is selected from the group consisting of a microRNA (miRNA), a small interfering RNA (siRNA), a short hairpin RNA (shRNA), a Piwi-interacting RNA (piRNA), phased small interfering RNA (phasiRNA), trans-acting siRNA (tasiRNA), a transfer RNA fragment (tRF), a small nuclear RNA (snRNA), transposable and/or retro-transpossable derived RNA, autonomous and non-autonomous transposable and/or retro-transpossable RNA.

10. The method of any one of claims 1-6 or 9, wherein said method further comprises introducing into the cell donor oligonucleotides.

11. The method of any one of claims 4-6, 9 or 10, wherein:

(i) said DNA editing agent comprises at least one sgRNA,

optionally wherein said DNA editing agent comprises an endonuclease,

optionally wherein said DNA editing agent is of a DNA editing system selected from the group consisting of a meganuclease, a zinc finger nucleases (ZFN), a transcription-activator like effector nuclease (TALEN), CRISPR-endonuclease, dCRISPR-endonuclease, and a homing endonuclease,

optionally wherein said endonuclease comprises Cas9; or

(ii) said DNA editing agent does not comprise an endonuclease,

and/or wherein said DNA editing agent is applied to the cell as DNA, RNA or RNP.

12. The method of any one of claims 5 or 9-11, wherein said target RNA of interest is endogenous or exogenous to said cell and/or wherein said specificity of said RNA molecule is determined phenotypically by determination of at least one phenotype selected from the group consisting of a cell size, a growth rate/inhibition, a cell shape, a cell membrane integrity, a tumor

size, a tumor shape, a pigmentation of an organism, a size of an organism, a crop yield, metabolic profile, a fruit trait, a biotic stress resistance, an abiotic stress resistance, an infection parameter, and an inflammation parameter.

13. The method of any one of claims 5 or 9-12, or genetically modified cell of any one of claims 7-9 wherein said cell is a eukaryotic cell, optionally wherein said eukaryotic cell is obtained from a eukaryotic organism selected from the group consisting of a plant, a mammal, an invertebrate, an insect, a nematode, a bird, a reptile, a fish, a crustacean, a fungi and an algae, optionally wherein said eukaryotic cell is a plant cell, and optionally wherein said plant cell is a protoplast.

14. A plant cell generated according to the method of any one of claims 1-6 or 9-13.

15. A plant comprising the plant cell of claim 14, optionally wherein said plant is non-transgenic.

16. A method of producing a plant with reduced expression of a target gene, the method comprising:

(a) breeding the plant of claim 15; and

(b) selecting for progeny plants that have reduced expression of said target RNA of interest, or progeny that comprise a silencing specificity in said RNA molecule towards said target RNA of interest, and which do not comprise said DNA editing agent,

thereby producing said plant with reduced expression of a target gene.

17. A method of producing a plant comprising an RNA molecule having a silencing activity towards a target RNA of interest, the method comprising:

(a) breeding the plant of claim 15; and

(b) selecting for progeny plants that comprise said RNA molecule having said silencing activity towards said target RNA of interest, or progeny that comprise a silencing specificity in said RNA molecule towards said target RNA of interest, and which do not comprise said DNA editing agent,

thereby producing the plant comprising the RNA molecule having the silencing activity towards the target RNA of interest.

18. A method of producing a plant or plant cell of claim 15 comprising growing the plant or plant cell under conditions which allow propagation.

19. The method of claim 16 or 17, wherein said breeding comprises crossing or selfing.

20. A seed of the plant of claim 15, or of the plant produced by the method of any one of claims 16-19.

21. The method or genetically modified cell of claim 13, wherein said eukaryotic cell is a human cell, optionally wherein said nucleic acid sequences encoding RNA molecules are selected from the group consisting of the nucleic acid sequences as set forth in any of SEQ ID NOs. 352 to 392 and/or wherein said eukaryotic cell is a totipotent stem cell.

22. A DNA editing agent for use in treating a disease in a subject in need thereof, comprising generating an RNA molecule having a silencing activity and/or specificity according to the method of any one of claims 1-6, 9-13 or 21, wherein said RNA molecule comprises a silencing activity towards a transcript of a gene associated with an onset or progression of the disease, thereby treating the subject.

23. A method of introducing silencing activity to a first RNA molecule in a cell, the method comprising:

(a) selecting a first nucleic acid sequence within said cell, wherein:

i. said first nucleic acid sequence is transcribed into said first RNA molecule within the cell;

ii. the sequence of said first RNA molecule has a partial homology to the sequence of a second RNA molecule, excluding sequence identity; wherein said second RNA molecule is processable to a third RNA molecule having a silencing activity; and wherein said second RNA molecule is encoded by a second nucleic acid sequence in said cell; and

iii. said first RNA molecule is not processable, or is processable differently than the second RNA molecule, such that the first RNA molecule is not processed to an RNA molecule having a silencing activity of the same nature as the third RNA molecule;

(b) modifying the first nucleic acid sequence such that it encodes a modified first RNA

molecule, said modified first RNA molecule being processable to a fourth RNA in the same way that said second RNA molecule is processable to the third RNA molecule, such that the fourth RNA molecule has a silencing activity of the same nature as the third RNA molecule,

thereby introducing a silencing activity to the first RNA molecule.

24. The method of claim 23, wherein said second RNA molecule is an RNA molecule which has a secondary structure that enables it to be processed into an RNA having a silencing activity, optionally wherein said silencing activity is mediated through engaging RISC, optionally wherein:

(i) said RNA molecule which has a secondary structure that enables it to be processed into an RNA having a silencing activity is selected from the group consisting of: microRNA (miRNA), short-hairpin RNA (shRNA), small nuclear RNA (snRNA or URNA), small nucleolar RNA (snoRNA), Small Cajal body RNA (scaRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), repeat-derived RNA, autonomous and non-autonomous transposable and retro-transposable element-derived RNA, autonomous and non-autonomous transposable and retro-transposable element RNA and long non-coding RNA (lncRNA); or

(ii) said first nucleic acid sequence results in a secondary structure which enables the modified first RNA molecule to be processed into the fourth RNA molecule, optionally wherein said modifying the first nucleic acid sequence comprises modifying the sequence such that the modified first RNA molecule has essentially the same secondary structure as that of the second RNA molecule, optionally a secondary structure which is at least 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or 100% identical to the secondary structure of the second RNA molecule,

or wherein said first nucleic acid molecule is a gene from *H. sapiens*, wherein the gene is selected from the group consisting of the genes having the sequences set forth in any of SEQ ID NOs. 352 to 392.