Claims

1. An isolated antisense oligonucleotide for inhibiting the expression of PRDM15 by inducing the skipping of an exon of a PRDM15 pre-mRNA or mature mRNA to induce cell cycle arrest or apoptosis~~modulating the activity of PRDM15~~, wherein the antisense oligonucleotide has any one sequence selected from SEQ ID NOs: 18, 19, 21, 26, 27, 36, 70, 71, 72 and 73, which specifically hybridises to a target region of a PRDM15 pre-mRNA or mature mRNA.

~~2. The antisense oligonucleotide according to claim 1, wherein the oligonucleotide modulates one or more of activity; or level of pre-mRNA, matured mRNA and protein expression.~~

~~3. The antisense oligonucleotide according to claim 2, wherein the oligonucleotide inhibits the expression of PRDM15 or modify its expression products.~~

~~4. The antisense oligonucleotide according to claim 3, wherein the oligonucleotide inhibits the expression of PRDM15 by inducing the skipping of an exon of a PRDM15 pre-mRNA or mature mRNA to induce cell cycle arrest or apoptosis.~~

~~5. The antisense oligonucleotide according to any one of the preceding claims, wherein the oligonucleotide specifically hybridises to a target region of a PRDM15 pre-mRNA or mature mRNA.~~

~~6. The antisense oligonucleotide according to claim 5, wherein the target region is any exon, intron or exon intron boundary selected from the group comprising: exon 8, exon 9, exon 11, exon 12, exon 15, exon 16, exon 17, exon 18, exon 21, exon 24, exon 25, exon 29, intron 7, intron 8, intron 11, intron 12, intron 14 and intron 15.~~

~~7. The antisense oligonucleotide according to any one of the preceding claims, wherein the antisense oligonucleotide comprises a sequence selected from any one of SEQ ID NOs: 1 to 73.~~

~~8. The antisense oligonucleotide according to any one of the preceding claims, wherein the antisense oligonucleotide comprises a modified polynucleotide backbone.~~

~~9. The antisense oligonucleotide according to claim 8, wherein the modified polynucleotide backbone comprises a modified moiety substituted for the sugar of at least one of the polynucleotides.~~

~~10. The antisense oligonucleotide according to claim 9, wherein the modified moiety is selected from the group comprising of phosphorodiamidate morpholino oligomer (PMO), peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO), and non-peptide dendrimeric octaguanidine moiety tagged morpholino oligomer.~~

~~11. The antisense oligonucleotide according to any one of claims 8 to 10, wherein the modified polynucleotide backbone comprises at least one modified internucleotide linkage.~~

~~12. The antisense oligonucleotide according to claim 11, wherein the modified internucleotide linkage comprises a modified phosphate.~~

~~13. The antisense oligonucleotide according of claim 12, wherein the modified phosphate is any one selected from the group comprising of a non-bridging oxygen atom substituting a sulfur atom, a phosphonate, a phosphorothioate, a phosphodiester, a phosphoromorpholidate, a phosphoropiperazidate and a phosphoroamidate.~~

~~14. The antisense oligonucleotide according to any one of preceding claims, wherein the antisense oligonucleotide comprises a backbone selected from the group comprising of ribonucleic acid, deoxyribonucleic acid, DNA phosphorothioate, RNA phosphorothioate, 2'-O-methyl oligoribonucleotide and 2' O methyl oligodeoxyribonucleotide, 2' O hydrocarbyl ribonucleic acid, 2'-O-hydrocarbyl DNA, 2'-O-hydrocarbyl RNA phosphorothioate, 2'-O-hydrocarbyl DNA phosphorothioate, 2'-F-phosphorothioate, 2'-F-phosphodiester, 2'-methoxyethyl phosphorothioate, 2 methoxyethyl phosphodiester, deoxy methylene(methylimino) (deoxy MMI), 2'-O-hydrocarby MMI, deoxy-methylphos-phonate, 2' O hydrocarbyl methylphosphonate, morpholino, 4' thio DNA, 4' thio RNA, peptide nucleic~~

~~acid, 3' amidate, deoxy 3' amidate, 2' O hydrocarbyl 3' amidate, locked nucleic acid, cyclohexane nucleic acid, tricycle-DNA, 2'fluoro-arabino nucleic acid, N3'-P5' phosphoroamidate, carbamate linked, phosphotriester linked, a nylon backbone modification and mixtures of the aforementioned backbones.~~

~~15~~2. The antisense oligonucleotide according to ~~any one of the preceding~~ claim~~s~~ 1, wherein the oligonucleotide is chemically linked to one or more conjugates that enhance the activity, cellular distribution, or cellular uptake of the antisense oligonucleotide.

~~16. The antisense oligonucleotide according to any one of claims 1 to 15 for use in treating a PRDM15 expressing cancer patient.~~

~~17. The antisense oligonucleotide according to claim 16, wherein the patient is administered a further anti-cancer agent or treatment.~~

~~18. The antisense oligonucleotide according to any one of claims 16 or 17 wherein the cancer is any one selected from the group comprising: haematological malignancies, lung cancer, breast cancer, prostate cancer, stomach cancer, testis cancer, larynx cancer, liver cancer, uterus cancer, colorectal cancer, melanoma, glioblastoma, sarcomas, and retinoblastoma.~~

~~19. The antisense oligonucleotide according to claim 18, wherein the haematological malignancies is either lymphoma or leukaemia.~~

~~20. The antisense oligonucleotide according to claim 19, wherein the lymphoma is a B-cell lymphoma.~~

~~21. The antisense oligonucleotide according to claim 20, wherein the B-cell lymphoma is a follicular lymphoma or a diffuse large B-cell lymphoma.~~

~~22~~3. A pharmaceutical composition comprising the antisense oligonucleotide according to any one of claims 1 ~~to 15~~or 2, and a pharmaceutically acceptable carrier.

~~23~~4. The pharmaceutical composition according to claim ~~22~~3, wherein the composition is suitable for parenteral administration either naked or complexed with a delivery agent to a patient.

~~24~~5. The pharmaceutical composition according to any one of claims ~~22~~ 3 or ~~23~~4, wherein the carrier is selected from the group consisting of a nanoparticle, such as a polymeric nanoparticle; a liposome, such as pH-sensitive liposome, an antibody conjugated liposome; a viral vector, a cationic lipid, a polymer, a UsnRNA, such as U7 snRNA and a cell penetrating peptide.

~~25~~6. The pharmaceutical composition according to any one of claims ~~22~~ 3 to ~~24~~5, wherein the antisense oligonucleotide is administered orally, or rectal, or transmucosal, or intestinal, or intramuscular, or subcutaneous, or intramedullary, or intrathecal, or direct intraventricular, or intravenous, or intravitreal, or intraperitoneal, or intranasal, or intraocular.

~~26. A method of treating cancer in a patient, the method comprising administering an antisense oligonucleotide according to any one of claims 1 to 15, or a pharmaceutically effective amount of a composition according to any one of claims 22 to 25.~~

~~27. The method according to claim 26, wherein the carrier is selected from the group consisting of a nanoparticle, such as a polymeric nanoparticle; a liposome, such as pH-sensitive liposome, an antibody conjugated liposome; a viral vector, a cationic lipid, a polymer, a UsnRNA, such as U7 snRNA and a cell penetrating peptide.~~

~~28. The method according to any one of claims 26 or 27, wherein the antisense oligonucleotide or composition is administered orally, or rectal, or transmucosal, or intestinal, or intramuscular, or subcutaneous, or intramedullary, or intrathecal, or direct intraventricular, or intravenous, or intravitreal, or intraperitoneal, or intranasal, or intraocular.~~

~~29. The method according to any one of claims 26 to 28, wherein the cancer is any one selected from the group comprising: haematological malignancies, lung cancer, breast cancer, prostate cancer, stomach cancer, testis cancer, larynx cancer, liver cancer, uterus cancer, colorectal cancer, melanoma, glioblastoma, sarcomas, and retinoblastoma.~~

~~30~~7. Use of an antisense oligonucleotide ~~that modulates the activity of PRDM15~~according to any one of claims 1 or 2 in the manufacture of a medicament for treating cancer.

~~31. The use according to claim 30, wherein the oligonucleotide modulates one or more of activity; or level of pre-mRNA, matured mRNA and protein expression.~~

~~32. The use according to claim 31, wherein the oligonucleotide inhibits the expression of PRDM15 or modify its expression products.~~

8. The use according to claim 7, wherein the cancer is a PRDM15-expressing cancer.

9. The use according to any one of claims 7 or 8, wherein the cancer is any one selected from the group comprising: haematological malignancies, lung cancer, breast cancer, prostate cancer, stomach cancer, testis cancer, larynx cancer, liver cancer, uterus cancer, colorectal cancer, melanoma, glioblastoma, sarcomas, and retinoblastoma.

10. The use according to claim 9, wherein the haematological malignancies is either lymphoma or leukaemia.

11. The use according to claim 10, wherein the lymphoma is a B-cell lymphoma.

12. The use according to claim 11, wherein the B-cell lymphoma is a follicular lymphoma or a diffuse large B-cell lymphoma.

13. The use according to any one of claims 7 to 12, wherein a further anti-cancer agent or treatment is administered.~~33. The use according to any one of claims 30 to 32, wherein the cancer is any one selected from the group comprising: haematological malignancies, lung~~

~~cancer, breast cancer, prostate cancer, stomach cancer, testis cancer, larynx cancer, liver cancer, uterus cancer, colorectal cancer, melanoma, glioblastoma, sarcomas, and retinoblastoma.~~

~~34. A method for aiding in categorising or determining prognosis in a patient with cancer, or in selecting a therapeutic strategy for a patient with cancer, the method comprising assessing the level of PRDM15 nucleic acid, protein or activity in a sample.~~

~~35. The method according to claim 34, further comprising the step of selecting a treatment regime making use of the information on the level of PRDM15 nucleic acid, protein or activity in the sample.~~

~~36. The method according to any one of claims 34 or 35, wherein the sample is obtained from the patient and the sample is a tissue sample in which cancer is suspected or in which cancer has been found, or contains cells from said tissue.~~

~~37. The method according to any one of claims 34 to 36 wherein if the level of PRDM15 nucleic acid, protein or activity in the sample is an elevated level, then the selected treatment regime comprises treating the patient with an inhibitor of PRDM15 activity or modulator of PRDM15's pre-mRNA, mRNA and protein expression levels.~~

~~38. The method according to claim 37, wherein the inhibitor or modulator comprises an antisense oligonucleotide according to any one of claims 1 to 15.~~

~~39~~14. A<u>n *in vitro*</u> method of inducing exon-skipping of a PRDM15 pre-mRNA, the method comprising delivering to a cell the antisense ~~polynucleotide~~ <u>oligonucleotide</u> of any one of claims 1 ~~to 15~~<u>or 2</u>~~, or the composition of any one of claims 22 to 25~~, thereby inducing exon-skipping of the PRDM15 pre-mRNA.

~~40. The method according to claim 39, wherein exons 12 and/or exon 15 is/are skipped.~~

~~41~~15. The method according to ~~any one of~~ claim~~s 39 or 40~~14, wherein the cell is a human cell.

~~42~~16. The method according to claim ~~41~~15, wherein the human cell is a cancer cell, the cancer is any one selected from the group comprising: haematological malignancies, lung cancer, breast cancer, prostate cancer, stomach cancer, testis cancer, larynx cancer, liver cancer, uterus cancer, colorectal cancer, melanoma, glioblastoma, sarcomas, and retinoblastoma.

~~43~~17. A kit comprising the antisense oligonucleotide of any one of claims 1 ~~to 21~~or 2, optionally in a container, and a package insert, package label, instructions or other labelling.